An Innovative Approach on Microemulsion: A Review

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ABSTRACT

Most pharmacological medications frequently exhibit poor dosage proportionality, significant intra- and inter-subject variability, and limited oral bioavailability when taken orally. It has been estimated that around 40% of innovative medication candidates don't dissolve very well in water. The development of a microemulsion drug delivery system may be the solution to the problem of how well lipophilic drugs work in the body (ME). A microemulsion is an idealised mixture of isotropic oils and surfactants, which may also comprise co-solvents. Microemulsions are also known as nano-emulsions. It is possible to make a fine oil-in-water emulsion on its own by pouring the mixture into the water phase and then gently swirling it around. The movement of the stomach and intestines that occurs during digestion makes it possible for in vivo emulsification to occur. The use of microemulsion is becoming more common and is essential in many different technological domains all over the world. These uses include oil recovery that is more economically feasible, combustion, cosmetics, pharmaceutical, agriculture, metal cutting, lubrication, food, enzymatic catalysis, organic and bioorganic processes, and more.

KEY WORDS: Oral delivery, Bioavailability, Lipophillic drugs, Microemulsion Drug delivery system.

1. INTRODUCTION

Effective oral drug delivery has been a challenge for the drug delivery industry for a very long time. This is due to the fact that more than 40% of innovative drug candidates have a low water solubility, and oral administration is often related with low bioavailability effects. Currently, a significant portion of novel chemical compounds, in addition to a great number of already existing medications, frequently have a low solubilizing capability. This frequently results in poor oral bioavailability with high individual and inter-individual variation, and it also presents significant technical hurdles for formulators. It is important to choose the appropriate dose form in order to avoid rendering useful drug ineffective due to inadequate distribution of the medication. 1 Surfactant(s) and microemulsions are both examples of systems that are anisotropic and thermodynamically stable. The dispersion domain diameter of these systems is typically between 10 and 50 nm, but may range anywhere from 1 to 100 nm. Microemulsions are liquid mixtures of oil, water, and a surfactant that are transparent, thermodynamically stable, and are often coupled with another surfactant. Microemulsions are also known as droplets or droplets of oil. The "oil" may be a complex mixture of various hydrocarbons and olefins, while the "aqueous phase" may include salt and/or other substances. Both phases, however, may be considered to be separate phases. 3 The following is an accurate explanation of what is meant by the term "microemulsions": "Microemulsions may sometimes be created when oil and water are mixed together. In addition, amphiphile is a liquid solution that has a similar appearance and is stable from a thermodynamic standpoint ". It is common knowledge that the addition of an appropriate surfactant can frequently result in large volumes of two incompatible fluids (such as oil and water) separating into a distinct phase that is microscopically heterogeneous but macroscopically homogenous. This phenomenon is known as phase separation mixture of active ingredients they are considered to be a member of the distinct group known as "microemulsions," which are defined as solutions that generally have a low viscosity, are transparent to light, and are thermodynamically stable[4, 5]. This method may be used to administer drugs that are either water-soluble or water-insoluble. It is possible to deliver pharmaceuticals that are water-insoluble by using oil-in-water (o/w) microemulsions, but it is also possible to administer medications that are water-soluble by using water-in-oil (w/o) microemulsions no more than one element each of the amphiphilic, hydrophilic, and associate types. [6] They are unlike ordinary emulsion, which is a square measure of thermodynamically unstable, in that they are naturally philosophically stable and possess a nanostructure. This is in contrast to regular emulsion, which is a square measure of thermodynamically unstable. [7] The microemulsions are see-through, and even with the most advanced optical magnification equipment; the structure of the microemulsions cannot be seen since the area of the elements is much smaller than the wavelength of the light being measured (400–800 nm). Due of this, microemulsions have a neat look and often have improved physical qualities in comparison to conventional emulsions. [8]

2. Microemulsion structure

Small-scale emulsions, often referred to as micellar emulsions, are a kind of energy system in which the interface fluctuates continuously and impulsively. Oil in water (o/w), water in oil (w), and bi-continuous microemulsions are the three structural subcategories of microemulsions. On a lesser scale, distributing water beads in a stage of continuous oil creates non-stop emulsions. On the other hand, when oil beads are dispersed in a stage of continuous water, oily microemulsions are created. When the proportion of water to oil in a structure is equal, the possibility of the formation of microdynamic emulsions, which are comprised of two continuous streams, exists. [10] Oil, water, and surfactants can form many different structures and phases, depending on their proportions. [11]

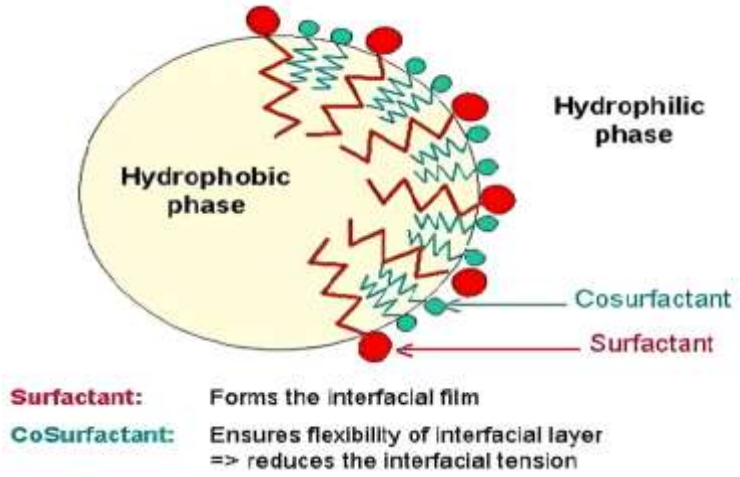

Figure 1: Microemulsion structure

3. History and Terminology

Prior to the research conducted by Hoare and Schulman in 1943, the concept of a microemulsion was unknown to everyone. They made the surprising discovery that the addition of a powerful surfactant allowed the water and oil to merge on their own. Even later, in 1959, Schulman et al.[12] introduced the term "microemulsion" to describe a multiphase combination combining water, oil, surfactant, and alcohol that generates a translucent solution. [13] This concept has sparked a significant amount of debate. Such systems are referred to as "microemulsions". Others choose the phrases "micellar emulsion" or "swollen micelles," despite the fact that these expressions are not used very often these days. Microemulsions were probably identified a long time before Schulman's study since Australian women have been using water, eucalyptus oil, soap flakes, and white spirit concoctions to wash wool since the turn of the previous century. It's likely that the liquid waxes found by Rodavald in 1928 were the first microemulsions to be used in commercial applications. In the late 1970s and early 1980s, when oil prices reached levels at

which tertiary recovery technologies were economically viable, there was an increase in interest in microemulsions. This interest was sparked by the realisation that such systems may potentially improve oil recovery. [15] In spite of the fact that this is no longer the case, microemulsions have found their way into 60 other processes, including the production of submicron particles, the conversion of solar energy, and the extraction of liquid from liquid (of minerals, proteins, etc.). In addition to its more typical applications in the sectors of detergents and lubricants, this industry is continuing to be large enough to attract a number of researchers. The basic study of the properties of microemulsions has seen substantial development over the last 20 years. This progress has been made possible by recent discoveries. [16]

4. CHARACTERISTICS

A separate oil-and-water system will be created when the right amount of a lipophilic and hydrophilic surfactant is applied. The system is still an emulsion, but it exhibits a number of characteristics that set it apart from previous reports of milk emulsions. These novel systems are referred to as microemulsions. The distinctions between emulsions and microemulsions include the interfacial tension between the phases, the amount of energy required for formation, the size of the droplet, and the appearance. Reverse micelles are another name for microemulsions made of water and oil. [17] Compounds that are both hydrophilic and hydrophobic may dissolve in these environments. Microemulsions often have low viscosities and Newtonian flow characteristics. The various shear rates have no impact on the flow through them. Discontinuous formulations could exhibit fluidity and plasticity that aren't Newtonian. The microemulsion has a viscosity that is similar to water's even at high droplet concentrations. These systems are very dynamic, and the fusing of droplets may happen in any direction since the microstructure is constantly moving. Several methods may be used to categorise microemulsions according to their distinct properties. There are other additional measures that are often utilised, including as light scattering, X-ray diffraction, ultracentrifugation, electrical conductivity, and viscosity. [18]

5. The difference between microemulsions and emulsions.

The structure and dimensions of the constituents that proliferate in an emulsion's constant phase are where one of the most significant distinctions between microemulsions and emulsions may be found. In general, this need is far shorter for microemulsions (ranging from 10-200 nm) than it is for the individual components of traditional emulsions (ranging from 1-20 micrometres). The microemulsions have a transparent or shining appearance, but the emulsions have a hazy appearance in the square size. This is still another significant distinction between the two. Due to the fact that emulsions need a significant amount of input energy, but microemulsions do not, the methods that are used to prepare them may be distinguished from one another in terms of their growth. [19]

6. Theories of Microemulsion Formation

Three different approaches have been historically used to explain the formation and stability of microemulsions.Interfacial or mixed film theories.

- Solubilization theories.
- Thermodynamic treatments.

One may reasonably assume that the free energy needed to form a microemulsion is proportional to the extent to which the surfactant modulates the system's entropy as well as the surface tension of the oil-water interface.

$$\mathbf{Gf = \gamma\ a - T\ S}$$

Where Gf = free energy of formation
A = change in the interfacial area of microemulsion
S = change in entropy of the system
T = temperature
γ = surface tension of oil-water interphase

It is crucial to note that a significant change in A occurs during the creation of the microemulsion as a consequence of the generation of a huge number of very small droplets. A negative number was required for the formation of a microemulsion (transient). It is well known that the value, although being consistently positive, is quite small and is counterbalanced by the entropy component. The main factor in the beneficial entropy is the exceptionally high entropy of dispersion, which results from combining two phases in the form of a massive number of tiny droplets. When one phase is combined with another, entropy is produced. On the other hand, it's predicted that additional dynamical processes like the diffusion of the surfactant in the interfacial layer and the interchange of the monomer-micelle surfactant would also result in positive entropy contributions. These procedures fall under the category of "dynamical processes." In light of this, it is possible to achieve negative free energy of formation when a major decrease in surface tension is followed by a significant and advantageous shift in entropy. This is the prerequisite for the emergence of negative free energy. Under these sorts of circumstances, the microemulsion naturally occurs and the result of that due the dispersion phase microemulsion found sthermodynamically stable. [20, 21]

7. Different types of microemulsions

Microemulsions can be thermodynamically stable even when created under particular conditions. Winsor says that there are four different phases of a microemulsion that happen when they are in equilibrium. These phases are also popularly known as Winsor phases. They are,

- Oil-in-water microemulsion or Winsor
- Water—in oil microemulsion or Winsor II
- Bicontinuous microemulsion or Winsor III
- Single-phase homogeneous mixture or Winsor IV

7.1 Oil-in-water microemulsion or Winsor

Although while microemulsions can only be produced under certain conditions, this does not mean that they cannot be thermodynamically stable. When it is in a state of equilibrium, a microemulsion will go through a total of four different phases, as described by Winsor. These stages are also sometimes referred to as Winsor phases. [22]

7.2 Water-in-Oil microemulsion or Winsor II

Water-in-oil microemulsions are surrounded by a continuous oil phase. The polar head groups of the surfactant are facing in the direction of the water droplets in these so-called "reverse micelles," whilst the fatty acid tails are pointing in the direction of the oil phase. An oral or parenteral water-in-oil microemulsion might be compromised as a result of the biological system that uses water. [23]

7.3 Bi-continuous microemulsion or Winsor III

Each part of a microemulsion system that doesn't stay together has the same amount of water and oil. In this scenario, water and oil exist side by side as two distinct phases. When water and oil are combined in an unequal channel, a phenomenon known as the "sponge-phase" may occur. During the process of changing from o/w to w/o microemulsions, it is possible for this bi-continuous condition to be crossed. There is a possibility that the bi-continuous microemulsion will display plasticity as well as non-Newtonian flow. Because of their properties, they are especially useful for the administration of medications by intravenous injection or topically. [24]

7.4 single-phase homogeneous mixture or Winsor IV

Mixing the oil, water, and surfactants evenly together makes a single-phase homogeneous mixture, which is also called a Winsor IV. .[25]

8. Advantages of microemulsion over other dosage forms.

1. Boosts the body's capacity for absorbing nutrients.
2. Cuts down on the amount of fluctuation in absorption.
3. Helps the lipophilic drug become more soluble by providing a helping hand.
4. Creates an aqueous dosage form for medications that are hydrophobic.
5. Increases the level of bioavailability.
6. There are a variety of routes available for administering the medicine, such as topically, orally, or intravenously.
7. Quick and effective distribution of the medicine across a certain region.
8. Helpful for concealing the taste of something.

9. Since the medication contained in the oil phase of the i/v microemulsion is not exposed to water or air, it is safeguarded against the processes of hydrolysis and oxidation.
10. The patient is more likely to take the medication when it is in liquid form.
11. Reduced amount of energy use. [25]

9. Disadvantages of Microemulsion Based Systems

1. The use of a wetting agent and additional surfactant in too high concentrations is critical to lighten the droplets of the microemulsion.

2. Limited solubilizing ability of drug used in the system.

3. The wetting agent must be non-toxic for pharmaceutical use.

4. The stability of the microemulsion is affected by environmental factors like temperature and pH. As the microemulsion is given to patients, these factors change. [26]

10. Limitations of the Microemulsion system

Because of the following factors, the use of microemulsion systems in the submission of pharmaceutical products is restricted: [27,28,29]

1. Phase separation is often a cause for worry in the context of microemulsions.
2. Because of the potential for toxicity, the concentrations of additional surfactants should be kept as low as possible.
3. Because of the toxicity of the formulation, microemulsion delivery methods are not well suited for intravenous administration, and there is presently a very little amount of research that has been published on them.
4. In order to reduce the toxicity of microemulsion systems, the surfactants that are used must be considered to be in the "generally safe" category.

11. Selection of components

Even though there are no clear rules for choosing the proper microemulsion components, selecting the surfactant is still a crucial step.

11.1 Aqueous stage

Commonly, the aqueous stage comprises preservatives and hydrophilic active components. Occasionally Buffer solutions are used as an aqueous stage.

11.2 Oil stage

Oil is an essential component of a microemulsion because it can dissolve the required dose of a lipophilic preparation. Oil is well defined as any liquid that consumes squats of polarity and the miscibility of squats with water. It also increases the proportion of the lipophilic drug excreted through the intestinal lymphatic system.

The surfactant(s) chosen must have:

1. In order to facilitate dispersion, the interfacial tension must be reduced to an extremely low value.
2. Thus, make a film that can bend easily and wrap around drops of water.

3. Provide the required interfacial curvature (HLB character) to create the proper microemulsion.

The surfactant used to stabilize the system can be of the following types:

1. Non-ionic: e.g. polyoxyethylene surfactants, such as Brij 35 or sorbita monooleate (span 80), polysorbates (80, 20, 60), Cremophore EL, Labrasol Triton X 100, Lauroglycol90, Labrafil M.
2. Zwitterionic: e.g. Phospholipids are a notable example that exhibits excellent biocompatibility.
3. Cationic: Quaternary ammonium alkyl salts form one of the best-known classes of cationic surfactants viz. hexadecyl tri methyl ammonium bromide (CTAB) and twin-tailed surfactant didcecyl ammonium bromide (DDAB).
4. Anionic: The most widely studied surfactant is ProbablY bis-2- ethylhexylsulpho succinate (AOT) which is twin-tailed and is a particularly effective stabilizer of w/o microemulsions.[30]

11.4 Co-surfactants

The formation of microemulsions almost always involves the use of co-surfactants, and for the following reasons in particular:

1. They make it possible for the interfacial layer to be flexible enough to conform to the many curvatures that are necessary in order to manufacture a microemulsion from a wide range of different compositions.
2. By reducing the amount of stress at the contact, alcohols with shorter and medium chain lengths (C3-C8) make the interface more fluid.
3. It is common practise for a surfactant with an HLB greater than 20 to coexist with another surfactant in order to reduce the effective HLB of the surfactant to a value that falls within the range required for the microemulsion formulation. This is done so that the microemulsion can be successfully formulated.
4. The following is a summary of the several cosurfactants that are used in microemulsions on the most frequent basis:
5. Sorbitan monoleate, sorbitan monostearate, propylene glycol, 2-(2-ethoxyethoxy)ethanol (also known as Transcutol), propylene glycol, and propylene glycol monocaprylate are the ingredients in this formula (Capryol 90).[25,31]

12. Formation of Microemulsion[32]

At a given temperature and pressure, a ternary phase diagram will display the many phases that are possible as well as the equilibrium between those phases for a combination that has three different components. Each compositional point in the single-phase zone above the separation line will result in the formation of a microemulsion. In the formulations ternary phase diagram that's produced multiphase areas that are mostly composed of microemulsions that are either in equilibrium with organic phase and aqueous phase, or both, i.e. with Winsor-type systems. These microemulsions may have either an organic phase or both an organic phase and an aqueous phase in balance with one another.

Each system with a general structure in the two-phase area has two phases, which are represented by the endpoints of the "connecting line," or section created by phases m and n. Despite the identical coexisting phases (m and n), the relative volumes at each link site are different.

A system is invariant at a fixed temperature and pressure if it can coexist in three phases, one of which is WIII. The third section of the triple diagram has three-phase systems with the same composition and connecting lines to the two-phase regions on both sides. Triple diagrams flank these systems. This particular section of the triple diagram represents the third kind of region that may be found inside the diagram. This particular section of the triple diagram represents the third kind of region that may be found inside the diagram. Because of its triangular shape, the "tie85 triangle" denotes a region that contains three-phase invariant compositions.

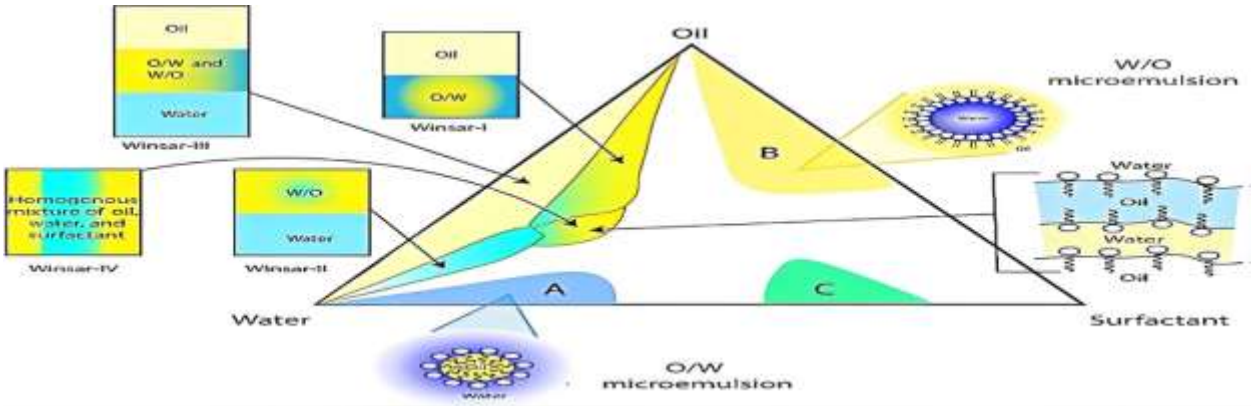

Figure 2: Formation of Microemulsion

13. Method of formulation[33,34]

Microemulsions have the potential to form if the interfacial tension present in an oil-and-water mixture is maintained at a very low level. Since the interfacial layer maintains its ability to be extremely flexible, the concentration of surfactant in the liquid has to be high enough for the molecules of surfactant to be able to stabilise the microemulsion even if the interfacial tension is very low. According to some sources, there are two primary methods for the production of microemulsions:

1. Phase Inversion Method

2. Phase Titration Method

13.1 Phase Inversion Method [35]

If too much of the phase being dispersed is introduced during the phase inversion process, the phase of the microemulsion will change. Rapid physical changes, including adjustments to particle size, occur during phase inversion. Phase transitions are the alterations that may affect drug release in both test tubes and living organisms. Oil/water microemulsion may change into a water/oil microemulsion at low temperatures, a process known as "transient phase inversion," which can be prevented by altering the temperature in the case of nonionic surfactants.

The system finally achieves a state where it has the lowest surface tension and zero spontaneous curvature as the cooling process proceeds. Little oil droplets may develop more easily as a result. The phase inversion temperature (PIT) technique is another name for this particular approach.

Additional parameters, besides temperature, could be seen as optional. Examples include salt content or pH value. In actuality, more than simply the temperature the spontaneous radius of curvature may also change if the volume proportion composed of water changes. Droplets of water initially appear in the otherwise continuous oil phase when more and more water is gradually added to the oil. The spontaneous curvature of the surfactant changes from initially stabilising water in oil microemulsion to forming oil in water microemulsion at the inversion point as the volume % of water in the combination increases.

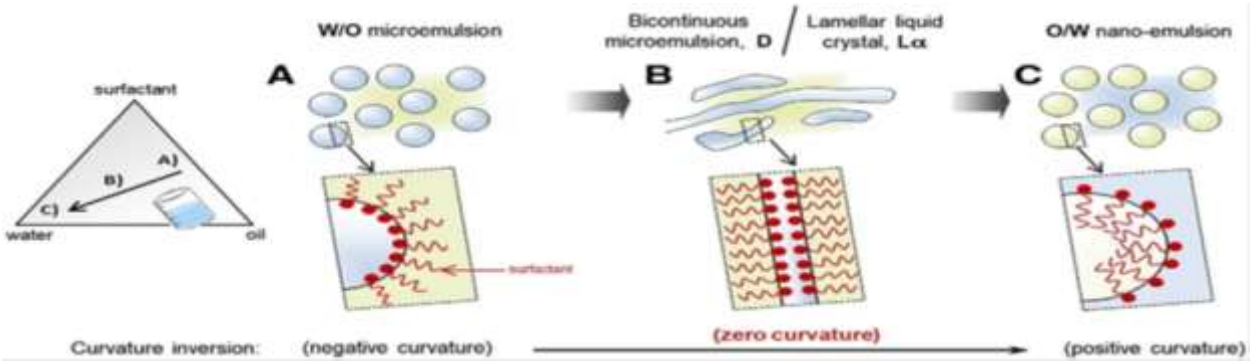

Figure 3: Phase Inversion Method

13.2 Phase Titration Method [36]

Phase diagrams show how spontaneous emulsification creates microemulsions (the phase titration technique). Fatty acids, oil, and alkali create a microemulsion. After correcting the co-surfactant concentration with titration, alcohol is added step-by-step until the system is clear. Microemulsion associative structures vary based on chemical composition and component concentration. These structures include oil dispersion, emulsions, micelles, lamellar, hexagonal, cubic, and various gels. Longer surfactant chains can create visible spectrum-transmitting microemulsions. Different alcohols also alter microemulsion growth. Short or branched alcohols yield the highest transmission rates and oil concentrations (dispersed in water).

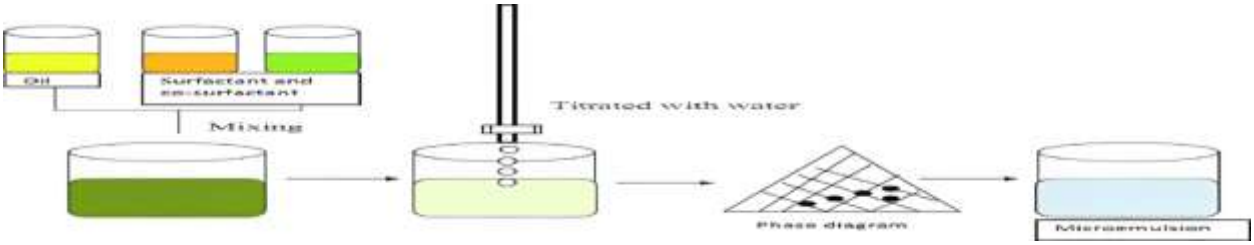

Figure 4: Phase Titration Method

14. Applications for using microemulsion in medication delivery

Microemulsions have been researched as a potential medication delivery method over the last 20 years because of its benefits, which include thermodynamic stability, optical clarity, and ease of penetration. This section's major subjects will be the function and use of the microemulsion as a medication delivery mechanism**.**

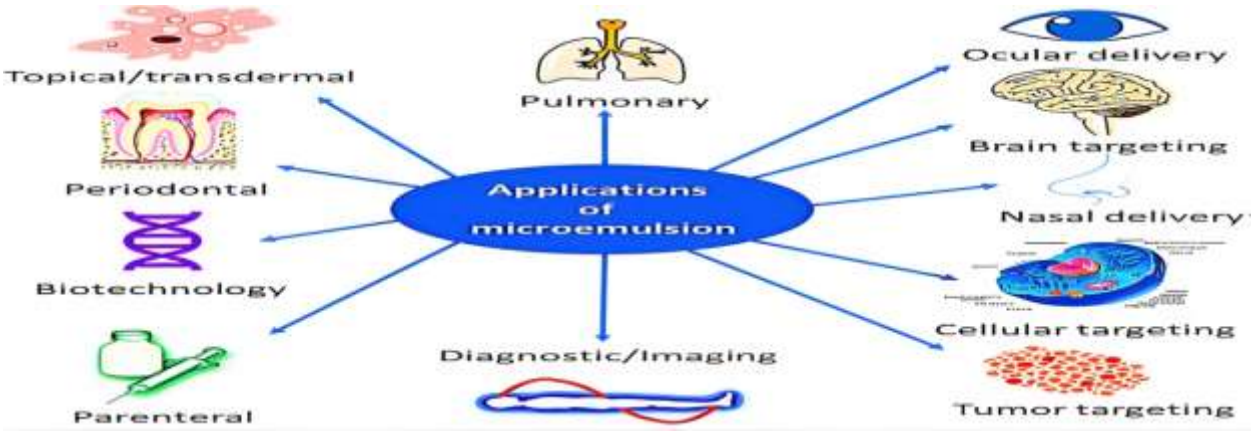

Figure 5: Applications of microemulsion in delivery of drug

14.1 Oral delivery

Researchers have struggled for a long time to create successful oral delivery techniques due to the fact that many drugs are either unstable or have poor dissolving qualities. This means that they do not dissolve or operate well in the fluid that makes up the stomach. Microemulsions may improve the solubilization of medications that are poorly soluble (especially BCS class II or IV pharmaceuticals), hence eliminating bioavailability issues brought on by dissolution. Different hydrophilic medications, including macromolecules, may be encapsulated with varied degrees of solubility since polar, nonpolar, and interfacial domains exist. The pharmaceuticals that have been integrated have been protected from oxidation, enzymatic degradation, and enhanced membrane permeability thanks to these mechanisms, which have been in place to protect them. Microemulsion formulations that are now available on the market include Sandimmune Neoral (R) (Cyclosporine A), Fortovase (R) (Saquinavir), Norvir (R) (Ritonavir), etc. Microemulsion formulation may be beneficial in boosting the oral bioavailability of some drugs because it improves the solubility of pharmaceuticals that are just slightly water-soluble in the fluid that is produced by the digestive system.[37]

14.2 Parenteral delivery [38]

Developing the parenteral dosage form of medications that are both lipophilic and hydrophilic has proven to be a challenging task. When it is not necessary to provide a suspension to the patient, O/w microemulsions are an effective alternative to suspensions for the parenteral delivery of medicines with low solubility. They make it possible to achieve a reasonably high concentration of these medications, which would normally need repeated dosing, making them an attractive alternative. They also have a better level of physical stability in plasma than liposomes or other vehicles, and the internal oil phase is more resistant to drug leaching than other vehicles. These are only some of the benefits that they provide. For the purpose of parenteral administration, some medicines with low solubility have been synthesised as oil-in-water microemulsions. In place of C3-C4 alcohols, the researchers Von Corse and Thoren38 adopted an alternative technique that included the use of parenterally acceptable co-surfactants. These co-surfactants included polyethylene glycol (400)/polyethylene glycol (660), 12-hydroxystearate, and ethanol. This was done with the objective of developing a middle phase

microemulsion that was almost perfectly balanced, all while keeping a flexible layer of surfactant and a very close to zero spontaneous curvature.

14.3 Topical delivery

Topical drug delivery provides a number of benefits over other methods of administration. One of these benefits is that the medication does not go through the liver's first-pass metabolism, which might make it poisonous. Another advantage is that the drug may be administered directly to the skin or eyes that are affected, enabling more precise therapy. In recent years, several studies on medication absorption via the skin have been conducted. They can hold both hydrophilic (like estradiol, finasteride, ketoprofen, meloxicam, felodipine, and triptolide) and lipophilic (like apomorphine hydrochloride, diphenhydramine hydrochloride, tetracaine hydrochloride, and methotrexate) drugs and make it easier for both types of drugs to get into the body. The possibility for skin irritation must be taken into account since the formation of microemulsions requires high quantities of surfactant. This is especially crucial if the microemulsions will be delivered over a prolonged period of time.[39]

14.4 Ophthalmic delivery

When it comes to conventional ocular dosage forms, pharmaceuticals that are water-soluble are often given in the form of aqueous solutions, whilst medications that are water-insoluble are typically supplied in the form of suspensions or ointments. These systems suffer from a number of significant flaws, the most significant of which are a lack of efficiency in the posterior area of the ocular tissue and a poor corneal bioavailability [40]. The creation of novel distribution systems that are much more successful than current ones has been the subject of recent study. For ocular applications, microemulsions have become a possible dosage form. The antibiotic chloramphenicol, which is used to treat trachoma as well as keratitis, hydrolyzes quite easily when it is included in conventional eye drops. Lv *et al.* tested eye drop drug delivery methods using a microemulsion of water, Span 20, Tween 20, and isopropyl myristate. Alcohol-free o/w microemulsions captured chloramphenicol. The hurried experiments showed that the microemulsion formulation had less glycol (the main hydrolysis product) than the commercial eye drops. Due to this, stable chloramphenicol in microemulsion formulations increased significantly. Fialho and colleagues examined forty microemulsion-based dexamethasone eye drops. The drops were more bioavailable and tolerable. The formulation reduced dosing frequency and improved patient compliance by increasing eye penetration.[41]

14.5 Nasal delivery

Microemulsions may help the nasal mucosa absorb more medicine. The mucoadhesive polymer also extends residency adhesion. Lianly et al. tested diazepam as an immediate status epilepticus therapy. At 2 mg kg1, diazepam was readily absorbed by the nasal and reached its maximal plasma concentration within 2-3 minutes.[42]

14.6 Drug targeting

The most coveted objective of medication delivery has been to target specific tissues with the medicine. Increase therapeutic effectiveness while reducing adverse effects by modifying the pharmacokinetics and biodistribution of the drug and restricting its action to the appropriate tissues. A new microemulsion formulation for the lipophilic antitumor antibiotic aclainomycin A was introduced by Shiokawa et al (ACM). They asserted that a folate-linked microemulsion may be used to deliver tumor-targeted ACM. Also, they discovered that by adding a suitable long PEG chain late in the process, emulsions may be effectively targeted to tumour cells.[43]

14.7 Brain Targeting

Intranasal administration is an easy method that is also practical, inexpensive, convenient, and non-invasive. It is used to ensure that medicine is delivered to the brain as quickly as possible. It is possible to circumvent the natural defences of the brain and deliver the drug directly to the brain. Vyas and colleagues developed a mucoadhesive microemulsion for the antiepileptic medicine clonazepam. This allowed for the medication to be more easily administered. The objective was to rapidly transport the drug to the brain of the rat. It was shown that the brain/blood ratio was 2-fold larger at all sample locations up to 8 hours later when clonazepam mucoadhesive microemulsion was administered intravenously. This finding suggests that the medicine was disseminated more broadly throughout the brain.[44]

15. Factors affecting the formation and phase behaviour of microemulsions

15.1 Factors affecting the formation of the microemulsion system [45]

The chain length, nature, and type of the co-surfactant, the packing ratio, the surfactant's property, the oil phase, temperature, and the packing ratio are just a few of the variables that can affect the production of an oil- or water-swollen microemulsion.

15.1.1 Packing ratio [46]

The kind of microemulsion is identified by the manner in which the HLB of the surfactant influences the manner in which the molecules pack together and the manner in which the film curves. The investigation of film curvature for surfactant linkages that contribute to microemulsion generation has been found as a critical packing property (CPP).

$CPP = v/a * l$ (3)

The ideal head group area is denoted by an, v is the symbol used to represent the partial molar volume of the hydrophobic component of the surfactant, and V is the symbol used to represent the length of the surfactant tail.

When CPP is more than one, the interface will spontaneously curve away from water (a negative curvature), which will favour the formation of microemulsions without water. When the CPP is between 0 and 1, the interface will bend in the direction of water (a positive curvature), as well as other o/w systems. When the HLB is balanced and there is no curvature, there is a possibility that bi-continuous or lamellar structures will emerge from the film if its stiffness is high enough (p equals 1) (zero curvature).

15.1.2 Property of surfactant, an oil phase, and temperature[47]

Multiple types of microemulsions may be created depending on the surfactant's function. A hydrophilic head group and a lipophilic tail group make up the surfactant. When defining the surfactant HLB in a particular system, the regions of these groups are essential for a specific formulation. These regions serve as a gauge for how differently water and oil tend to cause swelling in the head group and tail area, respectively. These components are used to gauge how differently water and oil tend to expand the head group and tail area, respectively. The head group has these parts. When the surfactant is used in large amounts or when it is combined with salt, the degree of polar group dissociation is reduced. As a result, the produced system is incapable of possessing a type. Water may encourage dissociation, which would lead to the development of an o/w system. Temperature has a significant impact on the characteristics of ionic surfactants. An increase in the dissociation rate of surfactant counter-ions is the most important result. The ability of the oil component to penetrate the surfactant monolayer and, as a direct consequence of this penetration, to enlarge the tail group area of the monolayer is one way that the oil component affects the curvature. Short-chain oils have the capacity to significantly penetrate the lipophilic group region, which will eventually lead to an increase in the negative curvature. Temperature is an essential issue for calculating the effective head group size of nonionic surfactants. They form a typical oil-in-water system at low temperatures because they are hydrophilic. They develop water-free systems as the temperature rises because they get lipophilic. If the microemulsion is heated to a temperature where it can live with the excess water and oil phases, it has the potential to form a bi-continuous structure.

15.1.3 The chain length, type, and nature of co-surfactant[48]

Co-surfactants made of alcohols are often used in microemulsions because of their solubility. Adding shorter chain co-surfactant has a favourable curvature influence and favours o/w type, Since alcohol swells the chain area more than the head region, adding a longer chain co-surfactant favours the w/o type. This is due to the fact that alcohol causes the head and tail to expand differently.

15.2 Factor affecting phase behavior

15.2.1 Salinity[49]

The low salinity causes an increase in the droplet size of the oil-in-water microemulsion. This is in line with the idea that there has been an increase in oil solubilization. As the salinity levels are increased further, the system transitions into a bicontinuous state throughout an intermediate salinity range. A continuous microemulsion that has smaller globules will form if there is an increase in the salinity. As the salinity of the water increases, a complete phase transition will occur over time.

15.2.2 Alcohol concentration[50]

When the quantity of the co-surfactant, low molecular weight alcohol, is increased, the microemulsion undergoes a phase change that transforms it from a w/o type to a bi-continuous type, and finally an o/w type. When a high-molecular-weight alcohol is present, the phase transition happens in the exact opposite direction.

15.2.3 Surfactant hydrophobic chain length [50]

The bi-continuous phase changes from an oil-in-water microemulsion to a water-in-oil microemulsion when the hydrophobic chain length of the surfactant grows.

15.2.4 pH [51]

Alterations in pH have an effect on microemulsions, particularly those that include surfactants that are pH-sensitive. When acidic or alkaline surfactants are used, the impact is magnified to a greater degree. The phase behaviour changes from water-like to water-like when the pH is raised by carboxylic acids and amines.

15.2.5 Nature of oil [51]

The phase shift from o/w to w/o is caused by a rise in oil aromaticity, which is the opposite of an increase in the alkane carbon number for oil.

15.2.6 Ionic strength[51]

When the ionic strength rises, the system goes through a series of transitions that begin with an o/w microemulsion that is in equilibrium with excess oil, then moves on to an intermediate phase, and finally concludes with a w/o microemulsion that is in equilibrium with excess water.

16. Evaluation parameters of microemulsion system

16.1 Physical appearance

It is possible to visually examine a microemulsion's homogeneity, fluidity, and optical clarity in order to assess the microemulsion's overall physical quality.

16.2 Scattering Techniques[52]

Small-angle neutron scattering, small-angle X-ray scattering, and light scattering are all types of scattering that can be used to study the structure of microemulsions. This is especially true when studying dilute monodisperse spheres. These methods are used to study systems that have a lot of different parts or are very concentrated, like those that are often found in microemulsions.

16.3 Limpidity Test (Percent Transmittance) [53]

A spectrophotometer may be used to perform spectrophotometric analysis to determining the microemulsion's degree of limpidity.

16.3 Drug stability[54]

The appropriate microemulsion being stored at ambient temperature, increased temperature ((50 ± 2°C), and cold circumstances (4–8°C). The microemulsion may be examined for phase separation, transmittance percentage, globule size, and assay percentage every two months.

16.4 Globule size and zeta potential measurements [55]

Dynamic light scattering is one method that may be utilised with a Zetasizer HSA 3000 to determine the globule size of the microemulsion as well as its zeta potential.

16.5 Evaluation of Rheological Properties (viscosity measurement) [56]

The stability of a system is significantly influenced by rheological characteristics. Using a digital viscometer developed by Brookfield is one way to find out. The ability to identify and distinguish the microemulsion zone from other parts of the system is made possible by a change in the rheological properties. The bi-continuous structure, the swollen reverse micelle, and the swelling micelles are all continually shifting in a bi-continuous microemulsion, which has a dynamic structure.

16.6 Electrical conductivity[57]

A conduct meter may be used to measure the electrical conductivity of the generated samples at room temperature with a fixed frequency of 1 Hz. Drop wise additions of the water phase were made to the mixture of oil, surfactant, and co-surfactant.

16.7 Drug solubility[58,59]

The enhanced microemulsion formulation included all of the components as well as an excessive amount of the drug. After a total of twenty-four hours of constant stirring at room temperature, samples were removed and centrifuged for ten minutes at a speed of six thousand revolutions per minute (rpm). The amount of soluble drug in the optimised formulation and the quantity of each element of the formulation were both calculated by first taking the total quantity of drug provided and then subtracting the amount of drug that was found in the sediment. The solubility of the medicine in the microemulsion was measured and compared to the solubility of the drug's individual components.

16.8 Constancy studies (Stability studies) [60-61, 72-86]

The ability of the microemulsion to retain its physical stability should be examined during the course of the year under various storage settings, including those with temperatures of 4, 25, and 40 degrees Celsius. Recent plans that used people in a similar way and had been held under various strain conditions with the purpose of enduring for a long time were jeopardised by the Droplet Dimensions Delivery Assessment. Calculations concerning the conclusion obtained about the surface-active agent and their focus on the drop's size also need to be made. [38]

16.9 pH of the Microemulsion[62, 63]

The sample tubes are used to collect various microemulsion samples. The pH scale of the individual samples is then checked using a micro pH metre. The bioavailability of the medication in the microemulsion and its consistency over the microemulsion by the permeation spot both rely on the pH scale of the preparation.

16.10 Transmittance examination [64]

After the implementation of the relevant dilution, investigators used an ultraviolet spectrophotometer to evaluate the consistency of the updated microemulsion formulation. The transmission at a certain wavelength was measured, and this allowed for the achievement of this goal.

16.11. In-vitro drug release [65, 66]

The Franz-Diffusion cell, which has been modified and has a capacity of 20 mL, is often used to conduct the diffusion research. The buffer was positioned in the cell's receptor area. The basic pharmaceutical solution and the microemulsion preparation were contained behind a plastic wrap

membrane that also served as the donor part's protection. An ultraviolet spectrophotometer operating at a certain wavelength was used to analyse the intermission trials from the receptor section to identify whether or not they contained any traces of medicine.

16.12. Identification test

Due to the fact that both forms of developed ME (w/o and o/w) seem identical to the naked eye, it is essential to do specific tests in order to detect which form of ME one has. Several experiments need to be carried out before one can draw a conclusive conclusion based on significant data. The kind of MEs may be identified once a series of essential diagnostic procedures have been carried out.

16.12.1 Dilution test

During a dilution test, either oil or water may be added in order to identify the kind of ME present (i.e., o/w or w/o). If water easily disperses in the continuous phase, then it is referred to as o/w ME; however, if oil is dispersed in the external medium, then it is referred to as w/o ME. The system is considered to be bicontinuous if the ME has been diluted with water or oil and has therefore become cloudy. 67 In addition, the phases of the resultant formulation will not break or separate even if the continuous phase, which is oil in the case of formulations without ME, is added to the ME. As a direct consequence of this, the formulation will maintain its stability, but water will keep on existing in its independent condition.

16.12.2 Dye solubility test

The kinds of MEs that are present are identified with this test. The combination is next put through a dye test, sometimes referred to as a stain test, in which an appropriate dye is sprayed onto ME. The water-soluble colourant (such methylene blue and amaranth, for instance) is integrated into the system in a relatively short period of time by utilising an o/w ME. The dye that does not include ME, on the other hand, creates clumps that may be seen under a microscope. Using an oil-soluble colour, on the other hand, will have the reverse effect. 68 For instance, if an oil-in-water ME is stained with a water-soluble stain, the backdrop of the MEs will be seen as blue (for methylene blue) or red (for amaranth) when the MEs are inspected under a microscope, but the globules will look colourless. This happens because the oil-in-water ME prevents the water-soluble stain from penetrating. [69]

16.12.3 Electrical conductivity test

The EC test is carried out in order to determine the nature of the ME, which may be either o/w or w/o. When there is no external phase of water present, such as in the o/w ME test, oil will conduct an electric current. Nevertheless, when there is an external phase of water present, oil will not conduct an electric current. This test is also used to determine whether or not the

emulsion has any phase inversions. When it comes to defining the structural and dynamic features of ME systems, the dielectric values are also quite important. [70]

16.12.4 Stability study

The International Conference on Harmonization recommends testing ME system stability in various storage settings. MEs samples can be examined for 12 months at 25 C62 C/60%65% RH or 3062 C/65%65% RH for long-term stability. For intermediate testing, samples are examined at 3062 C/65%65% RH for 6 months. The samples also undergo six months of accelerated testing at 4062 C/75%65% RH. Additionally, centrifugation stress testing and freeze-thaw cycles are performed. [71]

CONCLUSION

Microemulsions provide immense potential in terms of drug delivery and manufacture. The use of microemulsions in innovative solutions addresses the problem of highly oleophilic drug complexes' limited water solubility by enhancing bioavailability and making it more predictable and reproducible. The current research aims to provide complementing microemulsion components that are safe, inexpensive, and beneficial for these cutting-edge vehicles. Microemulsions are used to achieve targeted drug utilisation; nevertheless, there are still trials, primarily in the form of films, and challenges that these systems must overcome. Microemulsions may now be utilised to preserve active drugs, manage drug release, promote drug solubility and bioavailability, reduce patient variability, raise absorption rates, help in the dissolution of lipophilic pharmaceuticals, and offer and improve patient adherence. As a consequence, the use of microemulsion-based delivery systems is the most appealing and relevant area of study, providing both too many trials and maybe unexpected relief.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ABBREVIATIONS

^{0} C	=	degrees Celsius
Ml	=	Millilitre
nm	=	Nanometer
kg	=	kilogram
BCS	=	Biopharmaceutics Classification System

HLB = Hydrophilic–lipophilic balance
% = Percent
RH = Relative Humidity

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

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