Review Article

Microemulsions: New vista in novel drug delivery system

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ABSTRACT

Microemulsions are the novel drug delivery system for the treatment of several diseases. These are an isotropic, thermodynamically stable transparent system of oil, water, and surfactant. They have a long shelf life, better drug solubilization, ease of preparation, and administration in a potential drug delivery system. These versatile systems are clear, colloidal dispersion of water, oil stabilized by surfactant and cosurfactant and provides the protection against oxidation, enzymatic hydrolysis. Nowadays, microemulsion is widely used for hydrophilic as well as lipophilic drug delivery as drug carriers. They have numerous applications due to their unique properties such as ultralow interfacial tension, large interfacial tension, thermodynamic stability, and ability to solubilize other immiscible liquids. Microemulsions have great significance both in basic research and industry. In addition to the oral and intravenous route, they are suitable for sustained and targeted delivery through the ophthalmic, vaginal, dental, pulmonary, and topical route. The main objective of the study was to developing such a delivery system to minimize the drug degradation and loss, to prevent harmful side effects, and to increase the bioavailability. Therapeutic use of the microemulsion includes optimization of the duration of action decreasing the dosing frequency, controlling the site of release and maintaining the constant drug levels. Microemulsions have wide applications in terms of drug delivery. In this review article, we discuss the advantages, disadvantages, applications, preparation, theories, characterization, and significances of the microemulsion.

Keywords: Advantages, bioavailability, microemulsion, novel drug delivery system

Introduction

Novel drug delivery system (NDDS) refers to the approaches, formulations, technologies, and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effects. It may involve scientific site-targeting within the body, or it might involve facilitating systemic pharmacokinetics; in any case, it is typically concerned with both quantity and duration of drug presence. Novel drug delivery is often approached through a drug's chemical formulation, but it may also involve medical devices or drug-device combination products. Drug delivery is a concept heavily integrated with dosage form and route of administration. NDDS is an advanced drug delivery system which improves drug potency, control drug release to give a sustained therapeutic effect, and provide greater safety; finally, it is to target a drug specifically to the desired tissue. NDDS is a system for delivery of drug other than conventional drug delivery system. NDDS is a combination of advanced technique and new dosage forms which are far better than conventional dosage forms.[1]

The term "microemulsion" refers to a thermodynamically stable, isotropically clear dispersion of two immiscible liquids, such as oil and water, and it is stabilized by an interfacial film of surfactant molecules. Surfactant molecules contain both a polar and non-polar group. Hence, they exhibit a very peculiar behavior, first, they get adsorbed at the interface, where they can fulfill their dual affinity with hydrophilic groups located in the aqueous phase and hydrophobic groups in oil or air and second, they reduce mismatching with solvent by micellization process.[2] The dispersed phase typically comprises small particles or droplets, with a size range of 5 nm–200 nm, and has very low oil/water interfacial tension. Since the droplet size is <25% of the wavelength of visible light, so microemulsions are transparent. The microemulsion is formed readily and sometimes spontaneously, generally without high-energy input. In many cases, a cosurfactant or cosolvent is used in addition to the surfactant, the oil phase, and the water phase. The concept of microemulsion was first introduced by Hoar and Schulman in 1943;[3] they prepared the first microemulsions by dispersing oil in an aqueous surfactant solution and adding alcohol

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as a cosurfactant, leading to a transparent, and stable formulation. The existence of this theoretical structure was later confirmed by the use of various technologies, and today definition given by Attwood: A microemulsion is a system of water, oil, and amphiphilic compounds (surfactant and cosurfactant) which is a transparent, single optically isotropic, and thermodynamically stable liquid.[4]

Difference between Emulsion and Microemulsion

Emulsions and microemulsions [Figure 1] are both stable dispersions of oil-in-water (O/W) and water-in-oil (W/O). Surfactants have the property that they are used as principal agents and they enable oil and water to mix. Emulsions are stable dispersions of immiscible liquids, but they are not thermodynamically stable. The following properties show the difference between emulsion and microemulsions [Table 1].[5-8]

Types of Microemulsions

The microemulsions are three types, they are

1. O/W
2. W/O
3. Bicontinuous microemulsions.

[Figure 2] In O/W microemulsions, the volume fraction of oil is low conversely in W/O emulsion the volume fraction water is low and the oil droplets in O/W microemulsions are surrounded by the electrical double layer, which can extend into the external phase for a considerable distance up to 100 nm, depending on the electrolyte concentration.[9] In bicontinuous microemulsions, the amounts of water and oil ratios are similar.[10]

Winsor Classification of Microemulsions

Four different types of situations may arise by mixing oil, water, and amphiphiles as shown by Winsor.[11,12]

Type – I system

It consists of O/W microemulsions in equilibrium with the excess oil phase. The surfactant is preferentially soluble in water and O/W microemulsions form (Winsor I). The surfactant rich water phase coexists with the oil phase where the surfactant is used as monomers at small concentration.

Type – II

It consists of W/O microemulsions in equilibrium with excess water phase. The surfactant is mainly in the oil phase and W/O microemulsions form. The surfactant-rich oil phase coexists with the surfactant-poor aqueous phase (Winsor II).

Type – III

It consists of a microemulsion phase in equilibrium with both excess water and excess oil phase. A three-phase system in which a surfactant-rich middle-phase coexists with both excess water and oil surfactant-poor phases (Winsor III or middle-phase microemulsion).

Type – IV

A single-phase (isotropic) micellar solution that forms on addition of a sufficient quantity of amphiphile (surfactant plus alcohol).[13,14]

Significance of Microemulsion Over other Dosage Forms

1. Increase the rate of absorption
2. Eliminates variability in absorption

Figure 1: Emulsion and microemulsions preparation

Table 1: Difference between emulsion and microemulsions

Property	Emulsion (macroemulsion)	Microemulsion
Appearance	Cloudy	Transparent
Optical isotropy	Anisotropy	Isotropic
Interfacial tension	High	Low
Microstructure	Static	Dynamic
Droplet size	>500 nm	20–200 nm
Stability	Thermodynamically unstable	Thermodynamically stable and long shelf life
Phases	Biphasic	Monophasic
Preparation	Require a large input of energy	Facile preparation
Cost	Higher cost	Lower cost
Viscosity	High viscosity	Lower viscosity with Newtonian behavior
Turbidity	Turbid	Transparent
Cosurfactant used	No	Yes
Surfactant concentration	1–20%	>10%
Size range	0.5–5 u	0.1 u
Molecular packing	Inefficient	Efficient
Micelle formation	20 nm^{+}	3–20 nm
Contact position	Direct oil/water contact the interface	No direct oil in eater contact at the interface

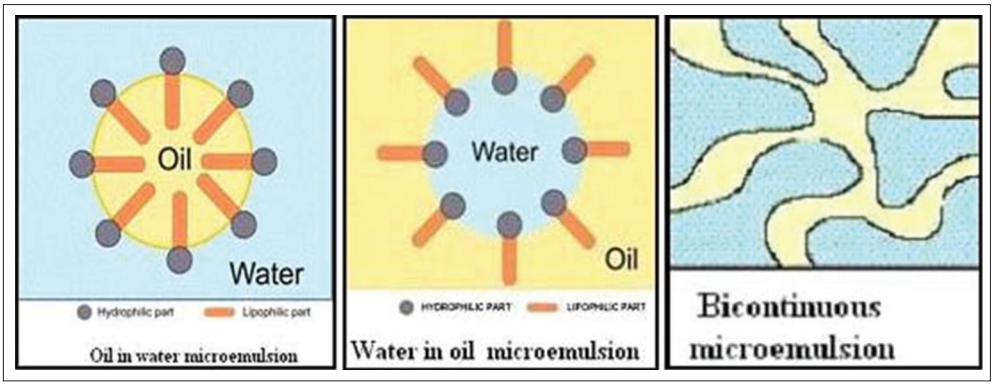

Figure 2: Types of microemulsions

3. Helps in the solubilization of lipophilic drug
4. Provides an aqueous dosage form for water-insoluble drugs
5. Increases the bioavailability
6. Various routes such as topical, oral and intravenous are used to deliver the product
7. Rapid and efficient penetration of the drug moiety
8. Helpful in taste masking
9. Provides protection from hydrolysis and oxidation
10. Increases patient compliance because of the liquid dosage form
11. Less amount of energy required.[15]

Theories of Microemulsions Formation

Historically, three approaches have been used to explain microemulsion formation and stability. They are as follows:

- Interfacial or mixed film theories
- Solubilization theories
- Thermodynamic treatments.

The free energy of microemulsion formation may depend on the extent to which surfactant lowers the surface tension of the oil-water interface and change in entropy of the system such that,

$$\Delta Gf = \gamma \Delta A - T \Delta S$$

Where, ΔGf = free energy of formation, ΔA = change in interfacial area of microemulsion, ΔS = change in entropy of the system, T = temperature, γ = surface tension of oil-water interphase. It should be noted that when a microemulsion is formed the change in A is very large due to a large number of very small droplets formed. For a microemulsion to be formed (transient) negative value of was required, it is recognized that while the value of is positive at all times, it is very small and it is offset by the entropic component. The dominant favorable entropic contribution is very large dispersion entropy arising from the mixing of one phase in the other in the form of a large number of small droplets. However, there are also expected to be favorable entropic contributions arising from other dynamic processes such as surfactant diffusion in the interfacial layer and monomer-micelle surfactant exchange. Thus negative free energy of formation is achieved when large reductions in surface tension are accompanied by significant favorable entropic change. In such cases, the microemulsion is spontaneous, and the resulting dispersion is thermodynamically stable.[6,16]

Advantages of Microemulsion System

- Microemulsions are easily prepared and require no energy contribution during
- preparation this is due to better thermodynamic stability
- The formation of the microemulsion is reversible
- They may become unstable at low or high temperature, but when the temperature returns to the stability range, the microemulsion reforms
- Microemulsions are thermodynamically stable system and allow the self-emulsification of the system
- Microemulsions have low viscosity compared to emulsions
- Microemulsions act as super solvents for drug can solubilize both hydrophilic and lipophilic drugs, including drugs that are insoluble in both aqueous and hydrophobic solvents
- Having the ability to carry both lipophilic and hydrophilic drugs
- The dispersed phase, lipophilic or hydrophilic (O/W, or W/O microemulsions) can act as a potential reservoir of lipophilic or hydrophilic drugs, respectively
- The use of microemulsion as delivery systems can improve the efficacy of a drug, allowing the total dose to be reduced and thus minimizing side effects.

Disadvantages of Microemulsions System

- Having limited solubilizing capacity for high melting substances
- Require a large amount of surfactants for stabilizing droplets
- Microemulsion stability is influenced by environmental parameters such as temperature and pH.9.[17-21]

Structure

Microemulsions are dynamic systems in which the interface is continuously and spontaneously fluctuating. In terms of structure, they are divided into O/W, W/O, and bicontinuous microemulsions. In W/O microemulsion, water droplets are dispersed in the continuous oil phase while O/W microemulsion is formed when oil droplets are dispersed in the continuous aqueous phase. In systems where the amounts of water and oil are similar, a bicontinuous microemulsion

may result. The interface is stabilized by an appropriate combination of surfactants and/or co-surfactants in all three types of microemulsion. The mixture of oil, water, and surfactants is able to form a wide variety of structures and phases depending on the proportions of the components. The flexibility of the surfactant film is an important factor in this regard. A flexible surfactant film will enable the existence of several different structures such as droplet such as shapes, aggregates, and bicontinuous structures, and therefore broaden the range of microemulsion existence. A very rigid surfactant film will not enable the existence of bicontinuous structures which will impede the range of existence. Besides microemulsions, structural examinations can reveal the existence of regular emulsions, anisotropic crystalline hexagonal or cubic phases, and lamellar structures depending on the ratio of the components. The internal structure of a microemulsion vehicle is very important for the diffusivity of the phases, and thereby also for the diffusion of a drug in the respective phases.[22,23]

Components of Microemulsion Based Gel

Oil phase

The selection of oil is based on the nature of the drug as well as the route of administration. The screened oil should have solubilization potential for the drug. The oil influences the curvature and has the capability to swell the tail group of surfactant. Saturated and unsaturated fatty acids have penetration enhancing activity of their own. Among unsaturated fatty acids, oleic acid is an effective skin penetration enhancer. A recent trend is toward the use of semi-synthetic oils that are more stable than their natural counterparts. Poorly aqueous soluble drugs need to have solubility in the dispersed oil phase to form efficient O/W microemulsion system. Even with the increase in oil content in O/W microemulsion leads to an increase in droplet size [Table 2].

Aqueous phase

The aqueous phase may contain hydrophilic active ingredients and preservatives. Water is most commonly used as an aqueous phase.

Surfactants

The primary use of surfactant is to lower the interfacial tension to a very small value which will facilitate dispersion process during the preparation of the microemulsion and provide a flexible film that can readily deform around the droplets and be of the appropriate lipophilic character to provide the correct curvature at the interfacial region. Surfactants used to stabilize the microemulsion system may be:

- Non-ionic
- Zwitterionic
- Cationic, or
- Anionic.

In the formation of microemulsion, the surfactant may be ionic or non-ionic, which determines the stabilizing interactions of the hydrophilic end of the surfactant with the aqueous phase. Thus, while a non-ionic surfactant is stabilized by dipole and hydrogen bond interactions with the hydration layer of water on its hydrophilic surface, an ionic surfactant is additionally stabilized by the electrical double layer. Thus, the effect of salt concentration on the stability of an emulsion or a microemulsion is more profound in the case of ionic surfactant than non-ionic surfactants. However, for pharmaceutical applications, ionic surfactants are not preferred due to toxicological concerns. Non-ionic surfactants are generally considered to be acceptable for pharmaceutical preparation.

It is generally accepted that low hydrophilic-lipophilic balance (HLB) (3–6) surfactants are favored for the formulation of W/O microemulsion, whereas surfactants with high HLB (8–18) are preferred for the formation of O/W microemulsion. Surfactants having HLB >20 often require the presence of cosurfactants to reduce their effective HLB to a value within the range required for microemulsion formation.

Table 2: HLB ranges and the typical application of surfactant related to it

HLB Value	Application
1–3.5	Antifoams
3.5–8	Water in oil emulsion
7–9	Wetting and spreading agents
8–16	Oil-in-water emulsions
13–16	Detergents
15–40	Solubilizers

HLB: Hydrophilic-lipophilic balance

Cosurfactants

It has been found that single-chain surfactants alone are unable to reduce the O/W interfacial tension sufficiently to enable a microemulsion to form. The presence of cosurfactants allows the interfacial film sufficient flexibility to take up different curvatures required to form microemulsion over a wide range of composition. 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). Short to medium chain length alcohols (C3-C8) are commonly added as cosurfactants, which further reduce the interfacial tension and increase the fluidity of the interface. Typical cosurfactants are short chain alcohols (ethanol to butanol), glycols such as propylene glycol, medium chain alcohols, amines, or acids.

The role of a cosurfactant is as follows,

1. Increase the fluidity of the interface
2. Destroy liquid crystalline or gel structure which would prevent the formation of a microemulsion
3. Adjust HLB value and spontaneous curvature of the interface by changing surfactant partitioning characteristic.[24-27]

Phase Behavior

The relationship between the phase behavior of mixture and its composition can be confined with the support of the phase diagram. The phase behavior of simple microemulsion systems comprising oil, surfactant, and cosurfactant can be studied with the aid of ternary phase diagrams in which each corner of the diagram represents 100%

of the meticulous component. However, almost always in case of microemulsions, they contain an additional component as cosurfactant and/or drug. In the case where four or more components are involved, pseudoternary diagrams are constructed where a corner represents a binary mixture of two components as surfactant/cosurfactant, water/drug, or oil/drug.

Phase Rule

The phase rule enables identification of the number of variables depending on system compositions and conditions. It is depicted as,

$$F = C - P + 2$$

Where, F is the number of possible independent changes of state or degrees of freedom, C the number of independent chemical constituents, and P the number of phases present in system. The F value determines the system to be invariant, monovariant, bivariant, etc., depending on its value whether zero, 1, 2, or so on. At low surfactant concentration, there is a series of equilibria between phases, referred to as Winsor phases.

Preparation of Microemulsions

Following are the different methods that are used for the preparation of microemulsion:

- Phase titration method
- Phase inversion method.

Phase titration method

Microemulsions are prepared by the spontaneous emulsification method (phase titration method) and can be portrayed with the help of the phase diagram. As quaternary phase diagram (four component system) is time-consuming and difficult to interpret, pseudoternary phase diagram is constructed to find out the different zones including microemulsion zone, in which each corner of the diagram represents 100% of the particular components. Pseudoternary phase diagrams of oil, water, and cosurfactant/surfactants mixtures are constructed at fixed cosurfactant/surfactant weight ratios. Phase diagrams are obtained by mixing of the ingredients, which shall be pre-weighed into glass vials and titrated with water and stirred well at room temperature. The visual inspection is used to confirm the formation of the monophasic/biphasic system. In case turbidity appears followed by phase separation, the samples shall be considered as biphasic. In case monophasic, clear and transparent mixtures are visualized after stirring; the samples shall be marked as points in the phase diagram. The area covered by these points is considered as the microemulsion region of existence [Figure 3].

Phase inversion method

Phase inversion of the microemulsion is carried out on addition of an excess of the dispersed phase or in response to temperature. During phase inversion, drastic physical changes occur, including changes in particle size that can ultimately affect drug release both *in vitro* and *in vivo*. For non-ionic surfactants, this can be achieved by changing

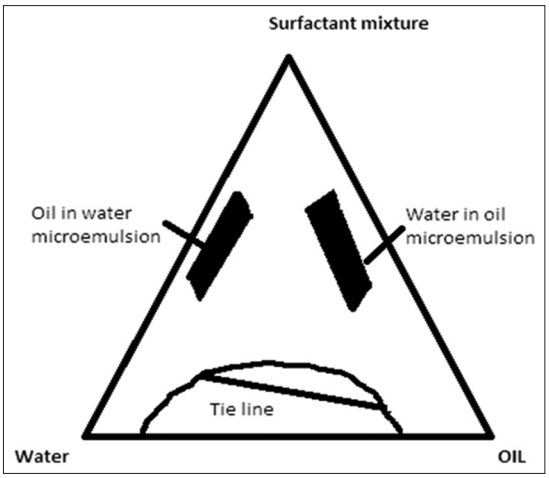

Figure 3: This represents a pseudoternary phase diagram

the temperature of the system, forcing a transition from an O/W microemulsion at low temperature to a W/O microemulsion at higher temperatures (transitional phase inversion). During cooling, the system crosses a point zero spontaneous curvature and minimal surface tension, promoting the formation of finely dispersed oil droplets. Apart from temperature, salt concentration or pH value may also be considered.[28]

Evaluation Parameters of Microemulsion System

Measurement of pH

The pH values of microemulsions were determined using digital pH meter standardized using pH seven and seven buffers before use.[29]

Limpidity test (Percent transmittance)

The limpidity of the microemulsion can be measured spectrophotometrically using a spectrophotometer.[30]

Drug stability

The optimized microemulsion was kept under cold condition (4–8°C), room temperature, and at elevated temperature (50±2°C). After every 2 months, the microemulsion can be analyzed for phase separation, percentage transmittance, globule size, and percentage assay.[31]

Globule size and zeta potential measurements

The globule size and zeta potential of the microemulsion can be determined by dynamic light scattering, using a Zetasizer human serum albumin 3000.[32]

Assessment of the rheological properties (viscosity measurement)

The rheological properties play an important role in stability. It can be determined by Brookfield digital viscometer. Change in the rheological

characteristics helps in determining the microemulsion region and its separation from other region. Bicontinuous microemulsion is dynamic structures with continuous fluctuations occurring between the bicontinuous structure, swollen reverse micelle, and swollen micelles. All the measurements were done in triplicate for 60 s at a temperature of 23.5°C.[33]

Electrical conductivity

The water phase was added dropwise to a mixture of oil, surfactant and cosurfactant and the electrical conductivity of formulated samples can be measured using a conductometer at ambient temperature and a constant frequency of 1 Hz.[34]

Polydispersity

This property is characterized by Abbe refractometer.[35]

Drug solubility

The drug was added in excess to the optimized microemulsion formulation as well as each individual ingredient of the formulation. After continuous stirring for 24 h 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 was calculated by subtracting the drug present in the sediment from the total amount of drug added. The solubility of the drug in microemulsion was compared with respect to its individual ingredients.

Phase behavior studies

Visual observation, phase contrast microscopy and freeze-fracture transmission, electron microscopy can be used to differentiate microemulsions from liquid crystals and coarse emulsions. Clear isotropic one phase system is identified as microemulsions whereas opaque system showing bifringence when viewed by crossploarized light microscopy may be taken as liquid crystalline system.[36]

Freeze-thawing method

Freeze-thawing was employed to evaluate the stability of formulations. The formulations were subjected to three to four freeze-thaw cycles, which included freezing at −4°C for 24 h followed by thawing at 40°C for 24 h. Centrifugation was performed at 3000 rpm for 5 min. The formulations were then observed for phase separation. Only formulations that were stable to phase separation were selected for further studies.[37]

In vitro drug release

The diffusion study can be carried out on a modified Franz diffusion cell, within the volume of 20 ml. The receptor compartment was filled with of buffer. The donor compartment was fixed with a cellophane membrane, containing the microemulsion formulation and the plain drug solution, separately. At predetermined time intervals, samples were withdrawn from the receptor compartment and analyzed for drug content, using a Ultraviolet spectrophotometer at a specific wavelength.[38,39]

Applications of Microemulsions in Delivery of Drugs

Microemulsions are promising delivery systems that allow sustained or controlled drug release for percutaneous, peroral, topical, transdermal, ocular, and parenteral administration. Enhanced absorption of drugs, modulation of the kinetics of the drug release, and decreased toxicity are several advantages in the delivery process.[40]

Microemulsions in ocular drug delivery

Eye drops are the most used dosage form by ocular route, in spite of low bioavailability and the pulsed release of the drug. However, due to their intrinsic properties and specific structures, the microemulsions are a promising dosage form for the natural defense of the eye. Indeed, because they are prepared by inexpensive processes through autoemulsification or supply of energy, and can be easily sterilized, they are stable and have a high capacity of dissolving the drugs. The *in vivo* results and preliminary studies on healthy volunteers have shown a delayed effect and an increase in the bioavailability of the drug. The proposed mechanism is based on the adsorption of the nanodroplets representing the internal phase of the microemulsions, which constitutes a reservoir of the drug on the cornea and should then limit their drainage.[41]

Microemulsions in cosmetic preparation

In many cosmetic applications such as skin care products, emulsions are widely used with water as the continuous phase. It is believed that microemulsions formulation will result in a faster uptake into the skin. Cost, safety (a many surfactants are irritating to the skin when used in high concentrations), and appropriate selection of ingredients (i.e., surfactants, cosurfactants, and oils) are key factors in the formulation of microemulsions.[42]

Microemulsions in biotechnology field

Many biocatalytic and enzymatic reactions are conducted in aqua-organic or pure organic as well as in biphasic media (i.e., polar media solubilizing enzymes and nonpolar media solubilizing polar substituents). Their use is seriously limited, as they can inactivate or denature the biocatalysts. Recently, interest on microemulsions is being focused for various applications in biotechnology, namely, enzymatic reactions, immobilization of proteins, and bioseparation.

The potential advantages of employing enzymes in media of low water content, i.e., W/O microemulsions are: (i) Increased solubility of non-polar reactants; (ii) possibility of shifting thermodynamic equilibria in favor of condensation; and (iii) improvement of thermal stability of the enzymes, enabling reactions to be carried out at higher temperature. Catalysis by a large number of enzymes in microemulsions media has been studied for a variety of reactions, such as synthesis of esters, peptides and sugar acetals; transesterifications; various hydrolysis reactions; glycerolysis; oxidation and reduction; and steroid transformation.[43]

Microemulsions in topical drug delivery

In conventional topical drug delivery involve either assisting or manipulating the barrier function of the skin (topical antibiotics, antibacterials, emollients, and sunscreen agents) or breaching the horny layer at the molecular scale so as to direct drugs to the viable epidermal and dermal tissues without using oral, systemic, or other therapies. Microemulsions have the ability to deliver larger amounts of water and topically applied agents into the skin than water alone or other traditional vehicles such as lotions or creams because they act as a better reservoir for a poorly soluble drug through their capacity for enhanced solubilization.[44] The role of penetration enhancers played by the amphiphilic components of the microemulsions and the internal mobility of the drug within the vehicle also contribute to the overall performance of microemulsions in dermal or transdermal drug delivery.[45]

Microemulsions in intranasal drug delivery

Intranasal microemulsions are one of the focused delivery options for non-invasive drug delivery to the systemic circulation. The researchers studied the brain uptake of nimodipine by intranasal administration of nonionic surfactant based microemulsions and found three-fold higher of nimodipine and higher ratios of the area under the curve (AUC) in brain tissues and cerebrospinal fluid to that in plasma.[46] In other studies, the intranasal delivery of microemulsions of sildenafil citrate showed shorter t_{max} and higher AUC compared to the oral tablets in rabbits and higher relative bioavailability of sildenafil citrate.[47]

Microemulsions in oral delivery

Microemulsions formulations offer several benefits over conventional oral formulation for oral administration, including increased absorption, improved clinical potency, and decreased drug toxicity. Therefore, microemulsions have been reported to be ideal delivery of drugs such as steroids, hormones, diuretic, and antibiotics peptides and proteins. However, most are difficult to administer orally and oral bioavailability in conventional (i.e., non-microemulsions based) formulation of <10%, they are usually not therapeutically active by oral administration. Due to their low oral bioavailability, most protein drugs are only available as parenteral formulations. However, peptide drugs have an extremely short biological half-life when administered parenterally, so require multiple dosing.

Microemulsions in parenteral drug delivery

Parenteral administration especially through the intravenous route of drugs with limited solubility is a major problem in industry due to the extremely low amount of drug actually delivered to a targeted site. Microemulsions formulations have distinct advantages over macroemulsion systems when delivered parenterally due to the fine particle Microemulsions is cleared more slowly than the coarse particle emulsion and, therefore, have a longer residence time in the body. Both O/W and W/O microemulsions can be used for parenteral delivery.[48]

Conclusion

Microemulsions are thermodynamically stable, possess excellent solubilization properties, and their formulation is a relatively straightforward process, so it is an interesting technology platform for the pharmaceutical formulator. These properties have their ability to incorporate drugs of different lipophilicity. Hence, the use of microemulsion is a most attractive and suitable area of research for drug delivery system, which is used to overcome many challenges and having extraordinary potential benefits. Recently, several research papers have been published for the improvement of drug delivery, but still, there is a need to emphasis on its characterization part including *in vitro* evaluation. Furthermore, it has proven possible to formulate preparations suitable for most routes of administration.

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