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Microemulsions and Micellar Systems as Increasingly Popular Carriers of Biologically Active Compounds and Drugs – Review

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Abstract

In the past and more recently, microemulsions containing biological compounds have increased the interest of researchers. They have shown great potential in cosmetics, medicines, detergents. They are also used in combinations of many natural/biocompatible compounds in the continuous or dispersed phase, which is otherwise challenging to formulate. Natural compounds are complex mixtures that contain compounds of different chemical nature; when combined in compounds and have universal therapeutic activity, they act alone or in combination with other compounds. In the present study, In this article, we intend to provide a summary of the structure and properties of microemulsion and micellar systems and their applications in various industries, including pharmaceuticals and food.

Keywords: Microemulsions; bio compounds; delivery systems; surfactants; micelles

Introduction

The three compound systems containing hydrocarbons, water, and emulsifying agents, also called surfactant's molecules depending on conditions, can form emulsion, microemulsions, nanoemulsions. Except for conditions under which these systems appear, they differ with the dispersed phase's droplet size. The emulsions are systems in which the average droplet size of the oil dispersion in water or water in oil ranges from ~0, 1 - 100 □m. In microemulsions, the suitable droplet size is in the range 0.0015- 0.15µm, and in nanoemulsions x10-9m. The nanoemulsions are very stable systems, transparent, and they can be obtained by mixing. Microemulsions are classified as durable systems and can be obtained by mixing also. Emulsions are cloudy and unstable systems that can be obtained by shaking. The surfactant and co-surfactant molecules introduced into such systems form the interfacial film stabilizing, especially microemulsion's structure. Belonging to the continuous and scatter phases, three basic microemulsions are known: direct (oil scatter in water, o/w), reversed (water distributed in oil w/o) bicontinuous. In 1959 Schulman et al. used it to describe the transparent system containing oil, water, surfactant, and alcohol [1]. Presently, such methods are called "micellar emulsion," micellar solution, or "swollen micelles".

A severe interest in microemulsion occurred at the end of the 20th century when it turned out that such systems could be used in petrochemistry, wastewater treatment, organic synthesis. After several years of interest in microemulsions and micellar solutions, it was found that these systems can be applied in extraction, catalysis, microreactors, drug systems delivery.

Discussions

Definition of "Microemulsions"

Conventional microemulsions are thermodynamically permanent, transparent, Newtonian, non-viscous liquids. They have an enormous solubilization capacity for other beverages or guest molecules like food additives, nutraceuticals, aromas, cosmetic compounds, active compounds, and drugs [2]. Microemulsions are good vehicles for solubilization and delivery of water and/or oil insoluble biologically active compounds. Microemulsions 1are used in several applications, including agriculture and food, drug solubilization, metal recovery, cosmetics, and beverages. Microemulsion systems may be misrepresented by the title "microemulsion." This claim is based on the description of an emulsion, which contains the term "inherently unstable"; however, "microemulsions" are inherently stable, by definition. In 2006 Flanagan and Singh's description primarily differentiated their systems from the macroemulsion systems, which were excellently studied at that course time [3]. An alternate moniker, or a name that defines a self-assembled, isotropic structure and thermodynamically stable, would be preferable to microemulsion. The initiation of a novel term to describe microemulsions would be confusing in light of other words (such as solubilized micellar solutions and swollen micelles), used to explain self-assembled, isotropic systems, and thermodynamically stable. Generally, although technically imprecise, it seems that the term "microemulsion" is here to remain. In 2011 Rao and McClements emphasize another terminology conflict: 'Some workers have challenged the efficacy of defining systems which contain either low volume portions of water or oil as microemulsions, suggesting that they should be referential as swollen micelles, and reserving the name of microemulsion for systems which have adequate dispersed phase incorporated into the surfactant micelles, such that the micelle can be considered to have the properties of its bulk. This is compared to the opinion that there is no diversity between swollen micelles and microemulsions. The term micellar solution should be maintained for self-assembled surfactant micelles in solution. Given the inner nature of 'sufficient dispersed phase,' these authors agree with Malcolmson et al. that thermodynamically stable, isotropic systems containing water, oil, and surfactant should be named microemulsions, and surfactant solutions should be called micelles or reverse micelles [4]. Microemulsions can dissolve large amounts of bioactive in the internal phase and interface because their ratio is too large. In addition to solubility, Microemulsions can act as carriers of the active substance through human membranes (intestines), which is very important in microemulsions systems. Of particular interest is the transport of biologically active compounds in food to the human organism and drugs, mainly insoluble in aqueous or poorly permeable systems. This review aims to outline current knowledge concerning the solubilization of bio compounds in microemulsions and to examine some new possible applications for microemulsions as microreactors and crystallization sites. It is challenging to comprehend general concepts to newcomers in the microemulsion field because research in this field is seldom systematic and based on thermodynamic rules. The researchers have used representative molecules and model systems and studied different features of solubilization and transfer. It should be emphatic that microemulsions have disadvantages. For example, microemulsions require comparatively high condensation of surfactants.

They are not suitable for some uses, such as food applications. In many cases, co-solvents (alcohol and polyols) are also needed, which are again considered inappropriate compounds. Attempts were made to use GRAS (generally recognized as safe) surfactants as components (mainly phospholipids), but these systems also have problems.

Surfactants and co-surfactants

Surfactants show unique properties when present at low concentration in a system containing unmixed liquids (i.e., water and oil). This exceptional property involves the accumulation (adsorption) of the particles of the surfactant on the surfaces (liquid/gas, usually air) or the interfaces (among two immiscible liquids) of the system. Thus, an altering to a marked degree of the level of interfacial free forces is observed. Measuring a liquid's surface tension, we estimate the interfacial free force per unit of the liquid's boundary and the air above it. Surfactants usually reduce interfacial free force, and in this way, stabilize the system liquid/air. The system consisting of two immiscible liquids like water and oil can be merged by introducing additional external energy (stirring, shaking, mixing). Finally, an unstable emulsion can be formed. Such unstable emulsion easily collapses to the two initial simple liquid phases. The surfactants were introduced into such an unstable system extending interface and significantly decreasing surface tension between the liquid phase. As a result, the system becomes to be stable and macroscopically transparent [5]. This unique property of surfactant molecules is because of a characteristic molecular structure called amphipathic. Amphipathic molecules consist of two parts: lyophilic/hydrophilic (polar) and lyophobic/hydrophobic/lipophilic (non-polar) (Figure 1)

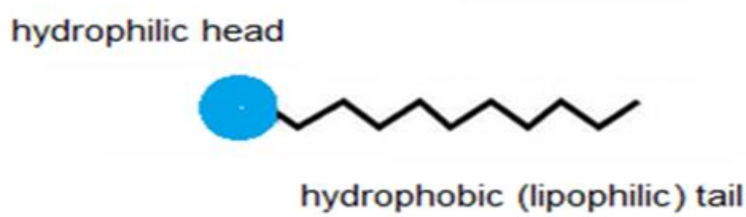

FIG.1. **Scheme of the surfactant molecule**

The surfactants are classified into a few groups depending on the type of polar head. There are anionic, cationic, amphoteric, zwitterion surfactants. The examples are shown in (Figure 2). Rosen has given the general structural features and physicochemical characteristic of surfactants in 2004 [6].

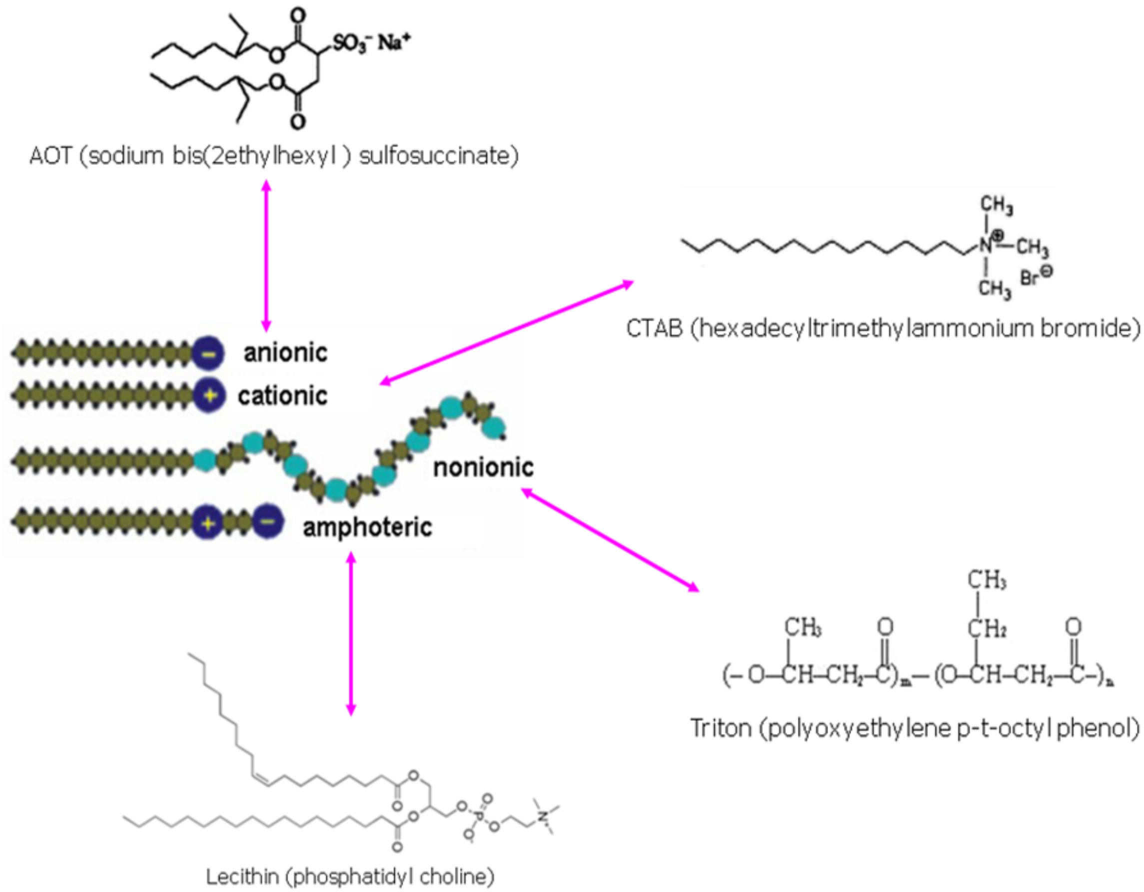

FIG.2. **Examples of surfactants belonging to different types.**

Except for surfactant, also so-called co-surfactant molecules introduced into such systems form the interfacial film stabilizing, especially microemulsion's structure. The interfacial film's curvature depends on the surfactant type and structure, as well as on temperature, oil to water phase ratio, and such factors as salinity, electrolyte presence in the systems, and others. The ionic surfactants containing single hydrocarbon toil (e.g., SDS sodium dodecyl sulfate) can aggregate to the micellar structures in the co-surfactant presence. Contrary to them, nonionic surfactants or ionic surfactants with double hydrocarbon toils (i.e., AOT) aggregate without the presence of co-surfactants. This ability of surfactant molecules to form the interfacial film between the dispersed droplets and dispersion phases relying on reducing the level tension between the water phase and the oil phase is the microemulsions micellar's fundamental property systems. This lowering level tension is sometimes enough to increase the level area so much that it is unnecessary to introduce external energy to the system, and the microemulsion forms spontaneously.

Microemulsions: Formation and Stabilization

The theories of "microemulsions" formation and stabilization are explained in brief here. For more details and information, the reader is directed to the research. The mixed film theory considers the interfacial film as a duplex film, having different properties on the water and oil side of the interface, which is zero interfacial tension. The solubilization theory states microemulsions as solutions with solubilized water or hydrocarbon: Which are considered to be one-phase systems. Microemulsions' thermodynamic theory suggests that the free force of formation, ΔGm, includes various terms, like interfacial free force. When ΔGm is of a very slight or little negative value, microemulsion formation can be facilitated [7]. Regardless of the mechanism of microemulsion stabilization, the reduction of the interfacial free energy to a meager amount is critical in simplifying "microemulsions" formation.

Phase behavior

Isotropic regions in a phase diagram are constructed based on the three major components in a system compound of the oil phase, surfactants phase (and possibly co-surfactant), and aqueous phase. Thermodynamically stable isotropic regions will form along with some phase diagrams. Mostly, at low oil concentrations (<30%), oil-in-water (o/w) microemulsions will form. Conversely, at low aqueous concentrations, water-in-oil (w/o) systems are developed. However, many different determining systems, such as micellar, reverse micellar, lamellar, and bicontinuous phases may exist at different oil-water-surfactant concentrations inside the specific o/w and w/o microemulsion areas. When there is no oil or water, micelles or reverse micelles may form the surfactant molecules through spontaneous self-assembly. All of them can exist, either alone or in composition with other systems, as transparent one-phase microemulsions. The boundary may be quite indistinct between microemulsion formation areas and areas outside the scope of one phase transparency. It may also coexist in balance with an excess of oil or water to single-phase microemulsions. These phases usually appear when there is an insufficient surfactant, and these multiphase systems are known as Winsor systems [8], and are illustrated in (Figure 3). The Winsor type systems contain an o/w microemulsion, which balances with an excess oil phase. Contrariwise, Winsor type II comprises a w/o microemulsion in balance with a lower different water phase. Winsor type III includes a microemulsion phase in balance with an excess aqueous phase and an additional oil phase. In 1988 Kunieda et al. proposed extending Winsor's classification with the fifth category of the degree in microemulsions. Finally, the single-phase systems already described (o/w, w/o, and bicontinuous) are Winsor type IV microemulsions.

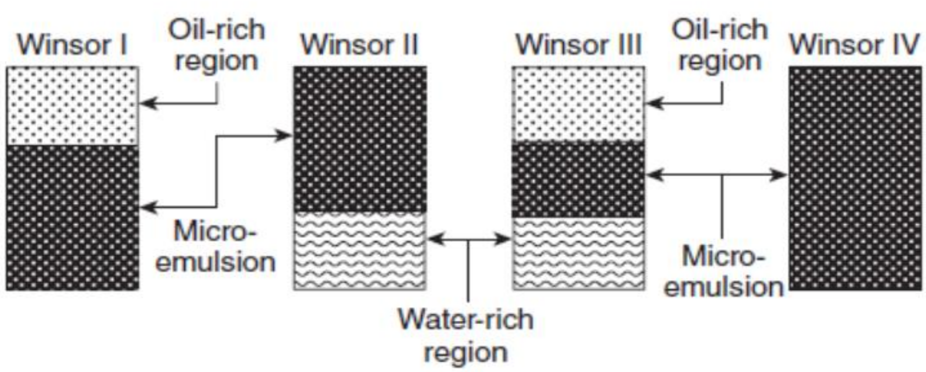

FIG.3.**Winsor classification system, showing oil- and water-rich phases possible in microemulsion systems. Redrawn with permission**

Materials and Methods

Methods of preparation of microemulsions

The microemulsion formation procedure depends on what type we want to obtain: water in oil (w/o) or oil in water (o/w). Usually, the process of microemulsion formation consists of two steps: (1) water, surfactant (and optionally co-surfactant) are placed together in a reactor and stirred until surfactant dissolves. (2) after, the mixture is titrated with oil until visually turbidity appeared. The opposite situation is also possible: (1) the mixture of water and oil is titrated with a surfactant solution until the whole mixture's turbidity disappears. The quantitative presentation of all mixtures (phase diagram) is usually shown on the Gibbs triangle. In such a ternary phase diagram, the surfactant and co-surfactant are classified as a single component. The literature in which authors present the typical and characteristic structures possible in a whole range of three-component phase diagram consisting of water/oil/surfactant is wide. Among many are single papers and books [9].

(a) Phase titration manner

(b) Phase inversion manner

There are the following steps:

- Dilution of the combination of an oil-surfactant with water > {W/O}
- Dilution of the water-surfactant mix with oil. [O/W]
- Mixing of all elements at once, in some systems, the instruction of components addition may specify whether a microemulsion forms or not

Nonionic surfactants like polyoxyethylene are susceptible to temperature. With temperature increasing, polyoxyethylene groups become dehydrated and consequently alter critical packing parameters, which results in phase inversion. The equipment used for the microemulsion preparation is a colloidal mill, rotor-stator, homogenizer.

Bioactive Natural Compounds

Mother Nature has been a source of medicinal agents for many centuries, and today 65% of the world's population relies on nature and its plants for their primary health care. A bioactive compound is a substance with biological activity that can negatively or positively affect a living organism, depending on the kind of importance, the dose, and their bioavailability. In general, it claimed that bioactive natural compounds in sufficient quantities could prevent or treat various diseases worldwide. Plants have many bioactive compounds; the significance of these biologically active constituents are alkaloids, flavonoids, tannins, and phenolic compounds [10]. These secondary metabolites have protective functions such as antibacterial, antiviral, antifungal, insecticide, and vegetarians with reduced their appetite for such plants. Many researchers claim that health benefits may be derived from incorporating bioactive combinations in food products, also known as functional foods. They are also known for heart disease debarment, immune system function, and cancer prevention. Also, β-carotene, curcumin, tocopherols, essential oils are the most lipophilic biological active compounds incorporated to fortify food. Microemulsions are exciting fields of utilization as they can act as carriers or transfer systems for bioactive compounds as flavors, antioxidants, anti-cancer, and antimicrobial agents. In general, they lead to improved consumer health.

Microemulsions as a delivery system of natural compounds/bio-compounds

Microemulsions have found wide applications in different human life areas, such as oil recovery, cosmetics, pharmaceutics, the food industry, and others. Besides, to use in everyday life, microemulsions have been applied in the science as simple models mimicking merely some structural aspects of biomembranes, in organic synthesis as mini reactors, and new areas appear. In the past, oil recovery was the main area of microemulsions applications. Then, due to studies on microemulsions' physicochemical properties, cosmetics, and the food industry, applications have been developed. In the previous century, pharmaceutics discovered new potential applications for microemulsions [11]. These specific micellar systems' specific properties are focused on scientists' investigations looking for developing excellent vehicles for drugs, foods, and pharmaceutics. The literature focused on microemulsions and micellar systems are pretty wide. It Is describes the outcomes of UV-vis, calorimetric, NMR investigations on biologically active compounds and systems mimicking structural aspects of parts of natural membranes like normal and reversed micelles. Generally, chemists' main attention focuses on finding the privileged location of natural compounds in the structure of micellar systems and estimating interactions between them [12]. The complete investigations evidenced that the strong limitations should be respected in the practical use of microemulsions or micellar systems in delivering drugs, bio-compounds, or foods. This is due to the standards for acceptable doses of surfactants in products intended for consumption. So, microemulsions and micellar systems still are useful for studies on different aspects of transportation, diffusion, releasing of drugs, food compounds [13]. This was the beginning of the progress of new systems models for membranes, particularly bio-membranes.

Nanoemulsions

Nanoemulsions are systems with a typical particle size between conventional emulsions and microemulsions, ranging from 50–200 nm. The small droplet size of nanoemulsions can affect properties such as particle stability, appearance, rheology, texture, and shelf life [14]. These systems are described as approaching thermodynamic equilibrium. Unlike microemulsions, nanoemulsions are not thermodynamically stable. They are kinetically stable and require much energy to produce. The droplets' net attractive forces are reduced by reducing the droplets' size, so the nano molecules show a lower tendency to droplet aggregation than conventional emulsions.

Microemulsion solution and increase bioavailability

The term bioavailability means the natural digestion, absorption, and metabolism of a particular nutrient. In general, the body absorbs a small number of compounds such as active peptides, carotenes, lycopene, curcumin, essential oils, omega-3 fatty acids, vitamins, and drugs. Because microemulsions are so small in size and therefore have a high surface-to-volume ratio, microemulsions and their components are absorbed faster from the gut compared to emulsions. The advanced dissolution of lycopene in O / W microemulsions increases bioavailability and adsorption in human tissues [15]. Studies show that microemulsions can be used to develop the oral bioavailability of drugs, including peptides. The bioavailability of β-carotene increased compared to the usual dispersion when administered in the shape of a microemulsion using a combination of surfactant monostearate and its polyoxyethylene form [16]. Medium-chain triglycerides act as absorption enhancers and increase the bioavailability of oils in human tissues. The increase in adsorption in different compounds depends on the kind of emulsifier, pH, the particle size of the dispersed phase, the kind of lipid phase, and the grade of solvability of the compound. The possibility of using microemulsions to enhance the attraction of different compounds, including oils, vitamins, peptides, and protein drugs, is often examined in pharmacological studies [17].

Highlights

The current short review presents how continuously and significantly grows the popularity of Micro emulsions and micellar systems as carriers of biologically active compounds and drugs in short way is evidenced the historical view of micro emulsions as vehicles of biologically active compounds the review article complements the lack of a specific view of micro emulsions presented by authors are given suggestion regarding micro emulsion's applications.

Conclusions

Today, research studies on the utilization of micro emulsions as carriers of natural compounds are expanding. Indeed, microemulsions containing natural compounds present many advantages, as previously mentioned in this review. Of course, there are also problems with the utilization of micro emulsions as a food delivery system. Difficulties in applying microemulsions are two-fold: restriction in the choice of appropriate surfactant and low solubilization of high molecular weight triglycerides. For example, the utilization of food-grade microemulsions in food belongs to the permissible limits of both the surfactant kind and surfactant concentration. Therefore researchers need to use surfactants that have been identified as GRAS for fundamental and applied research. Dilute micro emulsion systems that increase the solvability of lipophilic compounds in aqueous phases are being developed, which increases the application of microemulsions as a transfer system for bioactive compounds in various industries. It will also be interesting to create scientific research in vivo animals and humans after consuming functional foods fortified with bioactive compounds through microemulsion. Such studies would reveal the synergy among the bioactive compounds provided by the natural compound's resource and their carrier, such as microemulsion systems. That could also create new opportunities for collaboration between pharmaceuticals sciences and the food sciences for the next few years.

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