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Microemulsions: Unique Properties, Pharmacological Applications, and Targeted Drug Delivery

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Microemulsions, comprising oil, water and a surfactant, in association with some co-surfactant, are thermodynamically stable systems. They have found applications in a large number of chemical and pharmacological processes due to their unique properties such as large interfacial area, low interfacial tension, and most importantly, the ability to solubilize and deliver hydrophobic drugs. In addition to the oral and intravenous route, they are suitable for drug delivery through the ophthalmic, vaginal, pulmonary, dental, and topical routes. This review highlights the properties and several recent developments in the use of microemulsions for medical treatment purposes including targeted drug delivery.

Keywords: microemulsions, targeted drug delivery, biocompatible nanostructures, surfactants, self-emulsifying agents

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INTRODUCTION

Microemulsions comprise a special class of "dispersion" that may be transparent or translucent in appearance (Asua, 2014; Dixit & Mathur, 2015). They were first discovered by Hoar and Schulman (1943) in their experimental study of titration of long-chain fatty acids (soapy milky emulsions) with medium-/short-chain alcohols producing translucent or transparent system of emulsions. A schematic representation of the titration method adopted to produce is given below, which highlights the formation of transparent emulsion from water-in-oil (W/O) emulsion stabilized by long-chain fatty acids (soap) (Edser, 2011).

$$\text{W/O emulsion stabilized by soap} \xrightarrow[\text{e.g } C_5H_{11}OHC_6H_{13}OH]{\text{co-surfactant}} \text{Transparent or translucent}$$

A definition for microemulsion was provided by Danielsson and Lindman in 1981 as "a system of water, oil and amphiphile which is a single optically isotropic and thermodynamically stable liquid solution" (Danielsson & Lindman, 1981). Generally, microemulsions can be described as pseudo-homogeneous mixtures of water, water-insoluble organic compounds, and a mixture of surfactant/co-surfactant (Paveglio et al., 2021) (**Figure 1**). It is clearly evident from **Figure 1** that microemulsions can be prepared by mixing water, oil, surfactant/co-surfactant in different mixing ratios, considering the kind of microemulsion of either oil/water or water/oil. The amphiphiles (surfactant/co-surfactant mixture) lower the oil–water interfacial tension by interfacial adsorption, thus minimizing the positive free energy change of dispersion associated with the formation of a surface (Sharma et al., 2016).

Microemulsions are merely alike emulsions that are a different class of colloidal systems. We can observe colloidal systems in all three possible states of matter—gas, liquid, and solid.

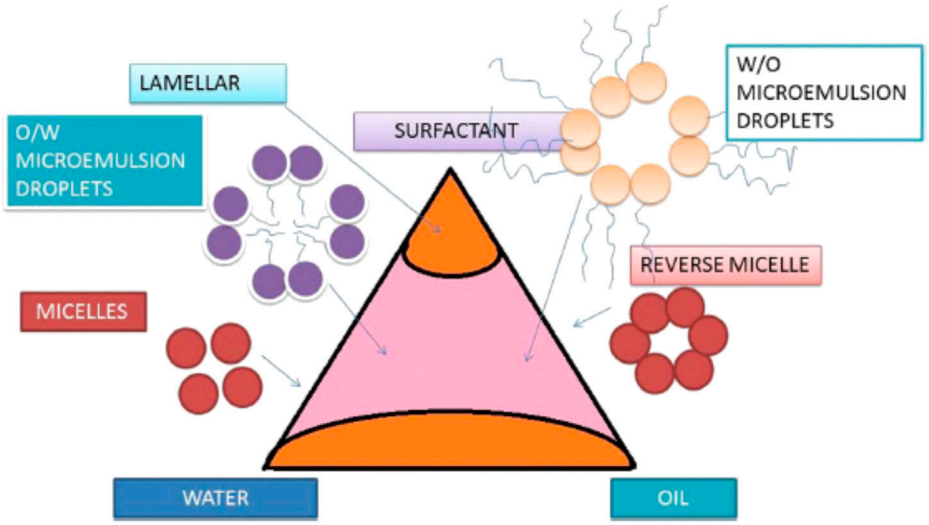

FIGURE 1 | Phase diagram of a microemulsion system.

Basically, the emulsions are formed via the emulsification of two or more immiscible liquids primarily.

The emulsions are basically formed from two or more immiscible liquid phases via emulsification, a profound characteristic of surface-active agents, making them versatile for a wide range of practical application, for instance, milk and cream, butter, margarine, mayonnaise, espresso, cutting fluid for metal working, and the photo-sensitizer (Kale & Deore, 2016).

PROPERTIES

There are two types of emulsions depending upon the size of the particles—emulsions having particle size in range of <0.5–50 μm are known as macroemulsions. These are easily visible under the microscope. The other type of emulsions is called microemulsion and has a particle size ranging from 10 to 200 nm (0.01–0.20 μm) (Schuster, 1996). Emulsions may be classified according to the structure of the system or the nature of the emulsifier (**Table 1**) (Schuster, 1996). Interestingly, the size of dispersed particles in an emulsion actually determines its appearance to the naked eye. If the diameter of the dispersed particle is 1 μm, the emulsion is milky white; 1–0.1 μm, blue white; 0.1–0.05 μm, gray, semitransparent; and <0.05 μm, transparent. Thus, macroemulsion is opaque, and microemulsion is transparent or semitransparent to visible light.

Depending upon the nature of the dispersed particles, microemulsions are classified into the following types:

1) Water-in-oil microemulsion

The W/O type microemulsion is a dispersion of water or an aqueous solution in a water-immiscible liquid. The water is, in this case, the "discontinuous" (inner) phase, and the oil is the "continuous" (outer) phase (**Figure 2**).

2) Oil-in-water microemulsion

The oil-in-water type is a dispersion of a water-immiscible liquid (always called the oil) in an aqueous phase. The oil is, in this case, the "discontinuous" (inner) phase, and the aqueous phase is the "continuous" (outer) phase (**Figure 2**).

3) Bicontinuous microemulsion

It consists of an infinite bilayer bent everywhere with a saddle-like curvature so that it is multiconnected to itself (by many random "passages" similar to tubular connections in the

TABLE 1 | Classification of emulsion types (Sweeta and Abdurahman, 2018).

Nature of emulsifier	Structure of the system	References
Nonionic surfactants	O/W, W/O emulsions	Cejka et al. (2007)
Ionic surfactants	Micellar emulsions	Cejka et al. (2007)
Surfactant mixtures	Microemulsions	Magzymov et al. (2016)
Polyelectrolytes	Bilayer droplets	Bera & Fang, (2012)
Mixed polymers and surfactants	Double and multiple emulsions	Zhao et al. (2018)
Liquid crystalline phases Solid particles (Pickering emulsions)	Mixed emulsions	Gonzalez Ortiz et al. (2020)

O/W, oil in water; W/O, water in oil.

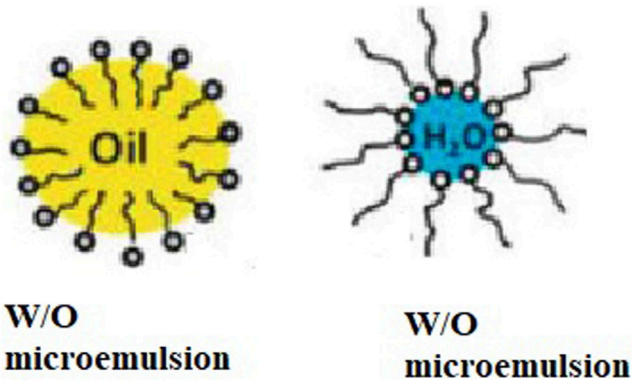

FIGURE 2 | Representation of different types of microemulsions.

FIGURE 3 | Schematic diagram of random connected bilayer network (Schuster, 1996).

sponge) isotropically over macroscopic distances and divides space into two independent solvents. Bicontinuous structures are present in the systems where the amount of water and oil is similar. Both the oil and water exist as a continuous phase in the presence of a continuously fluctuating surfactant-stabilized interface with a net curvature of zero (**Figure 3**) (Montalvo et al., 2001).

CHARACTERIZATION OF MICROEMULSIONS

The characterization techniques of microemulsions generally probe in at the macroscopic level, and microemulsions are generally evaluated at the macroscopic level via viscosity, conductivity, and dielectric measurement methods. The viscosity measurements probe in the micellar structure (Gukelberger et al., 2020; Majolino et al., 1990), the composition of emulsion is determined by conductivity measurements (Laguës & Sauterey, 1980; Pereira et al., 2016), and both the dynamic and detailed structural features of the emulsions are elucidated by dielectric measurements (Lian & Zhao, 2011; Weber & Stühn, 2016).

On the other hand, at the microscopic level, the optical clarity and isotropic nature of the emulsions are determined by spectroscopic techniques (Gao et al., 2006; Paul & Panda, 2014). A wide range of scattering techniques such as dynamic light scattering (DLS), static light scattering, small-angle X-ray scattering (SAXS), and small-angle neutron scattering (SANS) may provide detailed insight of the microstructure (Kaler et al., 1991; Lawrence & Rees, 2012; Paul & Panda, 2014). Nevertheless, the characterization of microemulsions is challenging due to inter particle-particle interactions due to the thickness of the solution, which needs statistical correction while measuring the droplet size accurately.

PHARMACOLOGICAL APPLICATIONS

Microemulsions have been studied extensively as potential drug delivery vehicles for poorly water-soluble drugs (Barot et al., 2012; Chudasama et al., 2011; Formariz et al., 2006; Hegde et al., 2014; Hu et al., 2011, 2014; Vinarov et al., 2018; Vyas et al., 2006) (**Table 2**). They are extensively being used as drug carrier systems for topical, oral, and parenteral administration of drugs, offering a variety of advantages such as ease of preparation, spontaneous formation and scale-up, thermodynamic stability, enhanced drug solubilization, and bioavailability. Microemulsions dramatically enhance the therapeutic efficacy of drugs and reduce the volume of the drug delivery vehicle, thus minimizing toxic side effects. The presence of surfactant as a major component of the microemulsion facilitates the drug absorption by elevating the permeability of cell membrane. Besides, in case of lipophilic drug administration, the ability of cell membrane to solubilize lipophilic component tremendously aids its absorption.

A new microemulsion-based system for a poorly water-soluble drug myricetin has been developed. Microemulsions protect the incorporated drugs from oxidative and enzymatic degradation. Examples include commercially available microemulsion formulations of cyclosporin A, saquinavir, and ritonavir (Fricker et al., 2010).

Microemulsions exhibit a high solubilization capacity for both lipophilic and hydrophilic drugs; thus, more drugs can be loaded into the microemulsion, which increases the concentration gradient across the skin without depletion. The reservoir effect of the internal phase maintains a constant driving force of drugs from the external phase to the skin and prolongs absorption. Since the diffusion of the drug into the skin only occurs from the external phase of the microemulsion, the internal phase continually supplies drugs to the external phase so that it remains saturated with the drugs (Fricker et al., 2010).

Oil-in-water (O/W) microemulsion systems are being used in the pharmaceutical industry with hydrophobic fluorocarbons (as oils) to produce short-time blood plasma substitutes to maintain the supply of oxygen in the living systems. The components that have been used include lecithins and non-ionic surfactants (Brijs, Arlacel 186, Spans, Tweens and AOT).

TABLE 2 | Recent research work on poorly soluble drugs.

Drug	Route of administration	Change in properties after incorporation in microemulsion	References
Flurbiprofen	Parenteral	Increased solubility	(Jadhav et al., 2008) 5(1):32–41
Apomorphine HCl	Transdermal	Enhanced permeability	Peira et al., (2001)
Ketoprofen	Transdermal	Enhanced permeability	Aliberti et al., (2017)
Prilocaine-HCl	Transdermal	Increased solubility	Sintov & Shapiro., (2004)
Estradiol	Transdermal	Increased solubility	Peltola et al., (2003)
Aceclofenac	Dermatological	Increased solubility	Yang et al., (2002)
Piroxicam	Oral	Increased solubility	Nazar et al., (2009)
Diclofenac	Transdermal	Enhanced permeability	Kizilbash et al., (2011)
Dexamethasone	Topical ocular	Enhanced bioavailability	Moghimipour et al., (2013)
Chloramphenicol	Ocular	Increased solubility	Lv et al., (2006)
Ibuprofen	Topical	Increased solubility	Hu et al., (2014)
Sumatriptan	Intranasal	Enhanced bioavailability	Vyas et al., (2006)
Doxorubicin	—	Increased stability	Formariz et al., (2006)
Itraconazole	Parenteral	Increased absorption	Chudasama et al., (2011)
Timolol	Ophthalmic	Increased absorption	Hegde et al., (2014)
Terbinafine	Transdermal	Enhanced permeability	Barot et al., (2012)
Fenofibrate	Self-microemulsifying	Increased solubility	Hu et al., (2011)
Progesterone	Dermal	Increased stability	Vinarov et al., (2018)

TARGETED DRUG DELIVERY

Various strategies have been employed to increase the pharmacokinetic properties via promoting the lymphatic transport; thereby, hepatic first pass metabolism can be surmounted. These strategies include complexation, pH modification, and use of lipid-based delivery systems. Among lipid-based formulations, self-microemulsifying formulations (droplet size <100 nm) have been shown to improve the pharmacokinetic properties of hydrophobic drugs primarily due to their efficiency in facilitating solubilization and in presenting the hydrophobic drug in solubilized form whereby the dissolution process can be circumvented (Akula et al., 2014; Alwadei et al., 2019; Atef & Belmonte, 2008; Kazi et al., 2021; Shahba et al., 2018).

The self-emulsifying system has gained exposure of its ability to increase solubility and pharmacokinetic properties of poorly soluble drug. Self-emulsifying drug delivery system (SEDDS) is an isotropic mixture of oil, surfactant, and co-solvent. SEDDS produces fine oil in water emulsion when introduced in aqueous media under gentle agitation. SEDDS-bound drug forms have been prepared for oral delivery for improved intestinal absorption of drugs. Forty percent of the newly discovered drugs possess little or low water solubility and hence minimal pharmacokinetic properties. These drugs are good candidates to be formulated in the form of self-microemulsifying drug delivery system (SMEDDS) (Gibaud & Attivi, 2012).

INFLUENCE OF PHYSICOCHEMICAL PROPERTIES ON CLINICAL STABILITY AND EFFICIENCY OF MICROEMULSIONS

The stability of parenteral emulsion is mandatory for administering them to the body. In contrast, instability of emulsions results in droplet cohesion and their separation, whereby the stability of the emulsions is strongly influenced by its physicochemical properties (Washington et al., 1993; McClements, 2007; Ishii & Sakurai, 2012; Schuh et al., 2014; Jacob et al., 2020). The physicochemical properties of parenteral emulsions directly depend upon a range of inherent factors such as composition and concentration of both hydrophilic and hydrophobic area, surface tension, pH of the medium, extent of dissociation, droplet size, electrical charge of the droplet surface, and their mutual interaction (Han et al., 2004; Hasan, 2019; Jacob et al., 2020). The surface electrical charge (zeta potential) of the emulsifier indicates its extent of dissociation. The higher the zeta potential, the higher would be the electrostatic repulsion between adjacent emulsion droplets leading to enhanced stability and vice versa (Fontana et al., 2016). Further, high surface tension is another desirable parameter of emulsions, which implies the homogenous dispersion of oil droplets in the emulsion leading to its stability. Among all of these properties, the mean diameter of the droplet is crucial to the parenteral emulsions, because large droplet size not only is prone to the hazard of emboli formation but also does not provide stability for longer circulation in the blood stream and, hence, is not desirable (Kawaguchi et al., 2008).

Several reports have been published to enunciate the correlation of physicochemical properties of microemulsion to their clinical stability and efficiency. For instance, Han et al. (Han et al., 2004) reported the successful preparation of stable emulsions of 2.5 mg/ml of paclitaxel using lecithin–sodium deoxycholate as an emulsifier mixture. The found excellent stability of the emulsion in plasma in the presence of polyethylene glycol as a stabilizer. Ishii et al. (Ishii & Sakurai, 2012) presented that 1.2% (w/w) lecithin emulsifier resulted in improved stability of emulsion in terms of zeta potential and mean diameter of the droplet. Shimokawa et al. (2017) observed a

clear dependence of droplet sizes of emulsions using three different kinds of emulsifiers (egg yolk lecithin, egg yolk lysolecithin, and a mixture of both) in relation to the pH of the medium. Kawaguchi et al. (2008) studied the effect of emulsifier on the stability of parenteral emulsion of phosphatidylcholine (PC-LM) in the presence of purified egg yolk lecithin (PEL) and observed desirable mean diameter of the droplet (250 nm) with good stability.

FUTURE DIRECTIONS

Microemulsions offer a wide range of applications such as targeted drug delivery, sustained drug delivery, controlled drug delivery, enzyme immobilization, enhancing bioavailability, and masking taste. Since orally delivered hydrophilic drugs are unstable in the gastrointestinal tract (GIT), new approaches must be found consisting of the use of biocompatible moieties for active targeting in clinical trials. Additionally, W/O microemulsions hinder the water-soluble drug molecules from being metabolized. W/O microemulsions, in addition to aqueous fluids, are converted to O/W microemulsions and, hence, release the active pharmaceutical ingredient (API), allowing the microemulsions to selectively release API to the targeted regions of GIT.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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