



Review

Microemulsion utility in pharmaceuticals: Implications for multi-drug delivery



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ABSTRACT

Emulsion technology has been utilized extensively in the pharmaceutical industry. This article presents a comprehensive review of the literature on an important subcategory of emulsions, microemulsions. Microemulsions are optically transparent, thermodynamically stable colloidal systems, 10–100 nm diameter, that form spontaneously upon mixing of oil, water and emulsifier. This review is the first to address advantages and disadvantages, as well as considerations and challenges in multi-drug delivery. For the period 1 January 2011–30 April 2016, 431 publications related to microemulsion drug delivery were identified and screened according to microemulsion, drug classification, and surfactant types. Results indicate the use of microemulsions predominantly in lipophilic drug delivery (79.4%) via oil-in-water microemulsions and non-ionic surfactants (90%) for oral or topical administration. Cancer is the disease state most targeted followed by inflammatory diseases, microbial infections and cardiovascular disease. Key generalizations from this analysis include: 1) microemulsion formulation is largely based on trial-and-error despite over 1200 publications related to microemulsion drug delivery since their discovery in 1943; 2) characterization using methods including interfacial tension, droplet size, electrical conductivity, turbidity and viscosity may provide additional information for greater predictability; 3) microemulsion drug delivery publications arise primarily from China (27%) and India (21%) suggesting additional research opportunities elsewhere.

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1. Introduction

1.1. Emulsion systems

Emulsion technology is utilized in a wide variety of industries including the cosmetic, agricultural, food and pharmaceutical industries (Bibette et al., 1999; Prince, 1977). Emulsions are metastable colloidal systems comprised of droplets of one liquid dispersed within another immiscible liquid (Rosen and Kunjappu, 2012). These two immiscible liquids themselves cannot mix and require the presence of emulsifying agents (emulsifiers) or surface-active agents (surfactants) (Rosen and Kunjappu, 2012; Leal-Calderon et al., 2007). Surfactants are amphiphilic in nature with a polar head and non-polar tail that orient at the interface of the water and oil phases, respectively, to reduce overall tension and promote miscibility. Fig. 1 depicts the orientation of surfactant molecules at an organic and aqueous interface.

In general, there are three main types of emulsion systems: (i) macroemulsions, (ii) nanoemulsions and (iii) microemulsions. The latter will be the primary focus of this article.

1.1.1. Emulsion types

The three main emulsion systems may be characterized based on their type, size, method of formation, and stability characteristics. These differences are summarized in Table 1 and depicted in Fig. 2.

1.1.2. Macroemulsions

Macroemulsions are often referred to as ‘coarse’ or opaque emulsions due to their relatively large droplet sizes which results in a turbid solution (Rosen and Kunjappu, 2012).

1.1.2.1. Type. In general, there are two main types of macroemulsions: oil-in-water (O/W) and water-in-oil (W/O). O/W emulsions consist of oil droplets dispersed in a water continuous phase while W/O emulsions consist of water droplets dispersed in

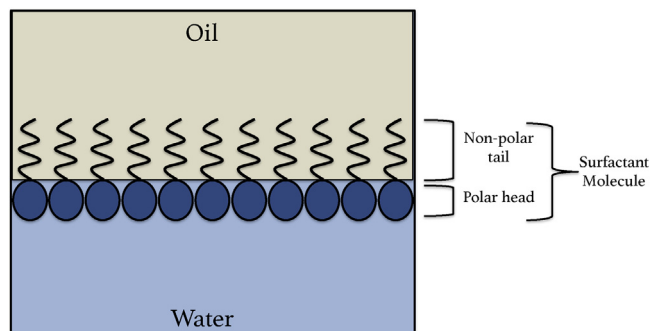


Fig. 1. Orientation of surfactant molecules at an oil-water interface. The polar head groups of the surfactant orient to face the polar, water phase while the non-polar tails groups of the surfactant orient to face the non-polar, organic phase. This type of orientation reduces the tension between the two interfaces promoting miscibility.

an oil continuous phase. In O/W emulsions, the water phase is referred to as the outer, continuous phase while oil is referred to as the inner, discontinuous phase (and vice versa). The two types of macroemulsions are shown in Fig. 3.

Macroemulsions may also be prepared as multiple emulsions. In particular, there are oil-in-water-in-oil (O/W/O) and water-in-oil-in-water (W/O/W) emulsions where the continuous phases are oil and water, respectively. Multiple emulsions are often used in delayed or controlled release formulations.

1.1.2.2. Size. In general, macroemulsions consist of droplets larger than 400 nm in diameter. These are significantly larger than the droplet sizes of micro- and nanoemulsions, often resulting in highly turbid solutions (Rosen and Kunjappu, 2012).

1.1.2.3. Formation. At a simple organic-aqueous interface, there is a difference in the potential energies between molecules in the bulk and molecules lying at the interface. Molecules lying at the interface possess higher potential energies as a result of their interactions not only with molecules of their respective phases, but also with molecules of the opposing liquid across the interface (Rosen and Kunjappu, 2012). This increase in potential energies represents the minimum work required to form the interface, or the interfacial tension.

Upon addition of an amphiphilic emulsifying agent or surfactant, the hydrophilic portions of the molecule orient themselves with the molecules of the aqueous phase (and vice versa for the hydrophobic portions with the organic phase). This results in stronger interaction energies between the amphiphile and respective phase in comparison to the system without an emulsifier. As a result, the overall interfacial tension is reduced. Without a surfactant, it is nearly impossible to sufficiently stabilize such a system. Where very low interfacial tensions are desired, co-surfactants may be added. Co-surfactants act in consort with surfactants to further reduce interfacial tension and introduce an element of flexibility into the interfacial film. This allows the system to adapt a wider variety of curvature values across an extended range of conditions for droplet formation (Talegaonkar and Negi, 2015). Medium chain alcohols or oils such as ethyl esters of fatty acids are usually used as co-surfactants as they reduce interfacial tension as well as introduce flexibility into the interfacial film (Talegaonkar and Negi, 2015). In addition, they may adjust the HLB value of the system by changing surfactant portioning characteristics, curb the formation of gel-like and crystalline phases which inhibit emulsion formation and decrease the sensitivity to fluctuations in structure (Talegaonkar and Negi, 2015).

The type of macroemulsion formed also depends heavily on the type of emulsifier used (Rosen and Kunjappu, 2012). O/W emulsions are produced by emulsifiers that are more soluble in water than oil, and vice versa (Bancroft, 1913). In other words, the continuous phase of any emulsion is dependent on the phase in which the emulsifier is most soluble. Several theories have been suggested for macroemulsion formation. Qualitative theories generally involve consideration of the interactions, i.e. interfacial

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