Chapter 5
Microemulsions as Antioxidant Carriers

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5.1 Introduction

Microemulsions have been known and investigated for more than 70 years since the introduction of pioneering works of Hoar & Schulman (Hoar and Schulman 1943) and Winsor (Winsor 1954). Even though these systems seem to be well known and thoroughly described, it is noteworthy that still they are gaining scientific attention regarding numerous interesting properties, which make them suitable for the application in many different areas. Among numerous research and industrial fields investigating the potential of microemulsions petroleum recovery (Nazar et al. 2011), nanoparticle synthesis (Wolf and Feldmann 2016), drug delivery (Callender et al. 2017), extraction processes (Ghouas et al. 2016) and novel cleaning technologies should be mentioned. Specific properties of microemulsions such as thermodynamic stability, extremely low interfacial tension and high interfacial surface, make their macroscopic features different from coarse emulsions and nanoemulsions. Moreover, because of the presence of surfactants (and sometimes co-surfactants), microemulsions display good solubilizing properties, which may be utilized in formulation and delivery of the substances with poor water solubility. The latter phenomenon is a frequently encountered problem in the studies related to the delivery of drugs and natural compounds, including antioxidants.

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5.2 Structure and Classification

Microemulsions are systems composed of polar and nonpolar phases stabilized with one or more surfactants. In order to decrease the interfacial tension to extremely low values, which is typical for these systems, usually a co-surfactant is required. Co-surfactant is a low molecular weight compound revealing weak surface activity. It is usually miscible with both oil and water phase which means it is localized not only in the interfacial layer but might be also present in both phases. Due to this property, it may be assumed that it can decrease the polarity difference between them and make the interfacial layer more flexible that contributes to the increased stability of the dispersion comparing to coarse emulsions and nanoemulsions. High flexibility of the interfacial layer and low interfacial tension induce high structural variability for microemulsions, which may occur not only as droplet systems but also as bicontinuous structures with hydrophilic and lipophilic domains intertwining each other (Fig. 5.1). The dispersed phase particles might adopt a shape different from spherical one, e.g. elongated ellipsoids (Lawrence and Rees 2012). One of

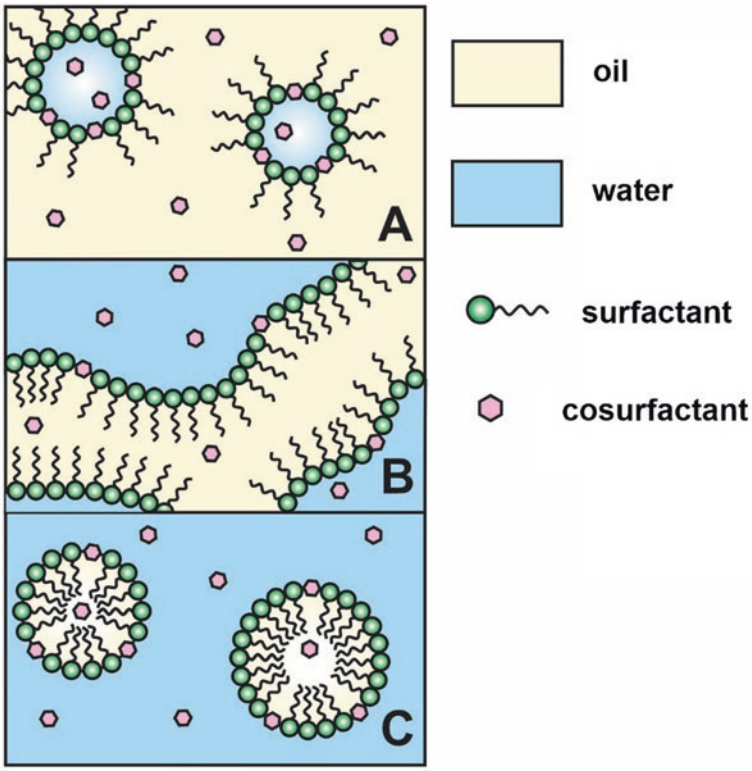

Fig. 5.1 Microemulsion structural types: (**a**) water in oil (W/O), (**b**) bicontinuous, (**c**) oil in water (O/W)

the most important factors determining the type of microemulsion is a quantitative relationship between polar and non-polar phases. The systems containing similar amounts of both phases tend to reveal bicontinuous structure while in other situations the prevailing phase tends to be a continuous (external) one. Another factor playing an important role in the formation of microemulsion is the characteristics of the interfacial layer, which is related mostly to the chemical and structural properties of the surfactant. One of the most popular parameters commonly used in the description of surfactant is hydrophilic-lipophilic balance (HLB) showing the ratio between polar and non-polar moieties in the surfactant molecule. The strong hydrophilic characteristic of surface-active agents is translated to high HLB numbers which usually leads to formation of O/W systems, while W/O microemulsions are formed by less polar surfactants with low HLB values. Another tool used in the description of microemulsion formation process is critical packing parameter (CPP, Eq. 5.1) reflecting the molecular geometry of the surfactant.

$$CPP = V / Al \tag{5.1}$$

where V is the partial molar volume of the nonpolar part of the surfactant molecule, A is the optimal polar head moiety area and l is the length of the hydrophobic chain (Lawrence and Rees 2012). In general, CPP adopts values smaller than one for the surfactants with more bulky polar head groups. In such cases, O/W microemulsions will be formed. Surfactants with large hydrophobic groups and CPP higher than one reveal the tendency to form W/O systems. When CPP = 1, lamellar systems and worm-like micelles might be formed. It is important to notice that the properties and curvature of the interfacial layer can be modified by the addition of other components, which can interact with surfactant molecules and participate in the layer formation.

It is important to notice that macroscopically microemulsions are perceived as transparent fluids displaying low viscosity. The definition formulated by Danielsson and Lindman in 1981 (Danielsson and Lindman 1981) allowed to differentiate between microemulsions and systems that are macroscopically similar but reveal different structure, such as liquid crystals, nanoemulsions and different micellar structures resulting from surfactant molecules association. According to the restrictions introduced by Danielsson and Lindman, microemulsions must be optically isotropic and thermodynamically stable liquids consisting of water, oil and amphiphilic component. Nevertheless, the term ‘microemulsion’ is still regarded as confusing and it is frequently used to describe for example submicron emulsions which might be kinetically stable but do not display thermodynamic stability (Anton and Vandamme 2011; McClements 2012). The most important systems similar to microemulsions are summarized in Table 5.1.

An important consequence of thermodynamic stability of microemulsions is their spontaneous formation without any significant amount of required energy. Taking into consideration the technological or industrial aspects of microemulsion manufacturing, the mentioned phenomenon is an enormous advantage because it excludes the necessity to apply expensive and energy-consuming high-shear

Table 5.1 The differences between microemulsions (ME) and similar systems

	System features						
System	Liquid	Oil	Water	Amphiphile	Thermodynamic stability	Isotropy	Droplet/ micelle diameter (Rao and McClements 2011)
Microemulsion	✓	✓	✓	✓	✓	✓	<100 nm
Nanoemulsion	✓	✓	✓	✓	×	✓	<200 nm
Coarse emulsion	✓	✓	✓	✓	×	✓	>200 nm
Micellar solution	✓	×	✓	✓	✓	✓	<100 nm
Liquid crystal/ lamellar phase	✓/×	✓	✓	✓	✓	×	No droplets

homogenizers or microfluidizing devices. The thermodynamic effects associated with microemulsion formation can be explained with Eq. 5.2 (Lawrence and Rees 2012):

$$\Delta G_f = \gamma \Delta A - T\Delta S \tag{5.2}$$

where ΔG_f is the free energy of microemulsion formation, γ is the surface tension, ΔA is the change of the interfacial area observed during the process, T is the temperature and ΔS is a change of entropy. Each spontaneous process is characterized by negative value of free energy. During microemulsion formation two significant changes in the parameters occur, i.e. increase of interfacial area and increase of entropy. Both of them are a result of the dispersion into numerous small droplets or domains. From the Eq. 5.1 it can be concluded that both described phenomena have an opposite effect on the free energy of the process. Therefore, to overcome the energetically unfavorable effects related to the increase of the interfacial surface, the interfacial tension value must be small. As it was mentioned above, in microemulsion this parameter assumes to be extremely low (close to zero), which explains spontaneous formation of these systems. Moreover, the described effects explain the necessity to employ co-surfactants to obtain microemulsions. Most of the commonly applied surfactants do not reveal the ability to decrease the surface tension at oil and water interface to extremely low values, so an additional element enhancing their action is required.

Considering microemulsion as a multicomponent system, it is important to note that it is not formed at any quantitative composition of oil, water, surfactant and co-surfactant. The same components may form structurally different systems, i.e. coarse emulsion, microemulsion and lamellar structure, depending on the concentrations of particular substances (Mouri et al. 2014). In order to establish the area of microemulsion occurrence, usually pseudoternary phase diagrams employing Gibbs triangle are used (Fanun 2008). However, graphical presentation of phase equilibria in the system containing four components with the use of three-dimensional space

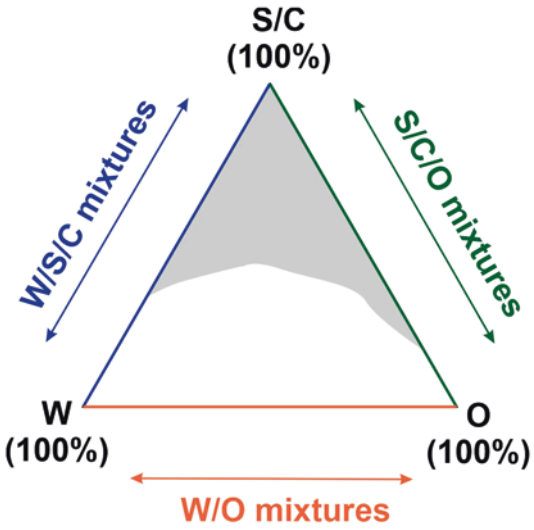

Fig. 5.2 Hypothetical pseudoternary plot for the system containing water (W), oil (O), surfactant (S) and co-surfactant (C). Gray area corresponds to transparent liquids identified as microemulsions, white corresponds to non-transparent coarse emulsions

requires some simplification. For this purpose, the mass ratio of two components is fixed and they are treated as one. As presented in the hypothetical pseudoternary phase diagram (Fig. 5.2), the corners of triangle are a graphical representation of three components (oil, water, surfactant/co-surfactant mixture at a fixed ratio). The points located in the sidelines correspond to the mixtures containing two components at different ratios. The closer to the particular corner the point is located, the higher the amount of this component in the mixture. The points present inside the plot contain all three components at different concentrations. The area corresponding to microemulsion occurrence is usually estimated with the use of titration experiment performed at fixed temperature and pressure conditions. In the first step, a set of binary mixtures at different ratios are prepared. Next, the mixtures are titrated with the third component. The systems which are low viscosity transparent liquids are classified as microemulsions (Djordjevic et al. 2004). The transparency loss indicates the transformation from microemulsion to coarse emulsion, while the increase of viscosity and gel formation can be interpreted as lamellar phase formation.

5.3 Applications

Microemulsions reveal numerous advantages making them useful for various practical applications in different scientific and industrial areas. It is important to note that they were used as household cleaning products long before the first scientific reports regarding their structure and properties were published. The first microemulsion-based products were used as washing and polishing liquids, usually containing natural oils and waxes and the first industrial formulations involving

microemulsions included cutting oils and lubricants. With the increasing popularity of nonionic surfactants in 1940s and 50s, microemulsions gained much attention also in other areas e.g. food, agrochemicals and paints industry (Solans and Kunieda 1997). Currently, the most important applications comprise tertiary oil recovery, drug delivery and analytical chemistry. It is also noteworthy that microemulsions still are acquiring a lot of scientific attention as extraction media or nanoreactor media for synthesis or templates for nanoparticles formulation.

5.3.1 Drug Delivery

One of the most important practical approaches involving microemulsions is the design and development of novel pharmaceutical formulations. It is important to note that in order to observe the therapeutic effect, the active pharmaceutical ingredient (API) must be absorbed either from gastrointestinal tract or from skin or mucous membrane surface. The absorption is possible only if either the drug is dissolved in an appropriate carrier or it can be dissolved directly at the absorption site. It is estimated that about 70% of newly synthesized APIs reveal low water solubility, which can be a potential problem in terms of therapeutic efficacy. Therefore, the design of a carrier allowing for the dissolution of the drug and enabling its efficient delivery is an extremely important part of pharmaceutical product development. Microemulsions are known for their high solubilization capacity both in the case of polar and nonpolar substances (Constantinides 1995). This phenomenon is a result of specific composition of microemulsions that usually contain relatively high amount of surfactant and co-surfactants, which can act as co-solvents for poorly soluble substances. Moreover, numerous studies indicate that microemulsions can be successfully employed as drug carriers improving bioavailability of active pharmaceutical ingredient. This effect was observed in various formulations, including oral, dermal ophthalmic and many other ones. In oral drug delivery particularly self-microemulsifying drug delivery systems (SMEDDS) should be mentioned (Kohli et al. 2010; Kuentz 2011). These systems are in fact in situ microemulsion-forming liquid mixtures of oil, surfactant and co-surfactant. After oral administration, the system is mixed with the fluid present in the gastrointestinal tract and because of its peristaltic movements, microemulsion is formed. It is noteworthy that these lipid-based formulations were successfully introduced to the pharmaceutical market and allowed for the significant improvements in the case of drugs with poor and variable bioavailability, and displayed significant differences in therapeutic effects observed inter- and intra-individually. Moreover, it was noted that incorporation of the drug in lipid-based formulation allowed for reduction of so called "food effects" related to the significant impact of the ingested food on the bioavailability of the drug administered orally (Pouton 2000; Perlman et al. 2008; Kohli et al. 2010). The mentioned phenomenon is observed mostly for strongly lipophilic drugs, which are absorbed more efficiently in the presence of dietary lipids, while in the fasting state the absorption is impaired.

Microemulsions are also considered as very efficient delivery systems for the drugs administered to the skin surface. Numerous studies reported usefulness of these systems in terms of overcoming the barrier function of *stratum corneum*, the external layer of the skin (Sintov and Shapiro 2004; Kogan and Garti 2006; Lopes et al. 2010; Gannu et al. 2010; Lopes 2014; Pillai et al. 2015; Aliberti et al. 2017). The exact mechanism underlying this phenomenon has not been precisely explained yet (Santos et al. 2008). However, there are several hypotheses that can describe it. One of them indicates high ability to improve the solubility of different drugs, which enables incorporation of higher amounts of active ingredients (He et al. 2010; Xing et al. 2016). As a result, higher concentration gradient between the formulation and skin is obtained, which allows for more efficient drug delivery. Another important feature of microemulsions frequently mentioned as a factor improving drug permeation through the skin is their composition. Surfactants and co-surfactants present in the formulation usually act as permeation promotors, temporarily disrupting lipid organization in *stratum corneum*. In the case of droplet-like O/W systems, the internal phase containing the drug may act as a reservoir. In such formulations, the active ingredient is transported continuously from the internal phase to the external one and the gradient between the formulation and the skin is maintained at the same level. Another factor important in terms of bioavailability of drugs incorporated in microemulsions is an extremely low interfacial tension that allows for good contact between the formulation and the skin. It is noteworthy that the droplet size in O/W and W/O systems seems to be of little importance in terms of skin permeation (Kreilgaard 2002).

Transparency and low viscosity of microemulsion make them interesting potential drug delivery systems for ocular delivery. Due to the aforementioned features, they can be spread easily at the surface of the eye without impairing vision. Moreover, they offer the possibility to transform into liquid crystalline system of increased viscosity upon the contact with tear fluid, which might provide prolonged drug release. This phenomenon seems to be particularly advantageous in ocular drug delivery because of specific physiology of the human eye and quick removal of the active ingredient with tear fluid that decreases the efficacy of conventional ocular drops instilled in the conjunctival sac. However, ocular drug delivery with the use of microemulsion-based systems might be challenging because of eye sensitivity and limitations related to the use of surfactants and co-surfactants. Similar problems may be encountered in the case of the drugs administered via parenteral route.

5.3.2 Petroleum Industry

Microemulsions have been investigated in the area of petroleum industry as well. Naturally occurring crude oil impregnates rocks and it is estimated that only 10–20% of the available resource can be effectively extracted with conventionally applied methods, such as drilling and pumping. In order to retrieve the remaining amount, some additional techniques must be applied. In secondary methods, water or steam

is used to push out the oil from its source and direct it to the wellbore. In enhanced oil recovery methods known also as tertiary techniques, oil is obtained with the use of various materials injected into the reservoir. In the process involving microemulsion, surfactant solution with some additives is used in order to decrease the interfacial tension between water and oil to reduce capillary forces. In this way, the oil can be displaced from reservoir rock. Extremely low interfacial tension observed in microemulsions, as well as their low viscosity, are regarded as useful features in terms of tertiary oil recovery (Santanna et al. 2009; Nazar et al. 2011; Bera and Mandal 2015).

5.3.3 *Microemulsion Electrokinetic Chromatography (MEEKC)*

Microemulsion electrokinetic capillary chromatography (MEEKC) is a separation technique that employs electrical current. The separation process takes place in a capillary filled with O/W microemulsion. Microemulsion droplets are stabilized by an anionic surfactant, which is usually sodium dodecylsulfate, and n-butanol as a co-surfactant. The droplets play the same role as the stationary phase in different chromatography techniques. As a mobile phase, aqueous buffer is applied. The technique can be used to separate various range of solutes, including charged and uncharged ones. The basic principle of the described method is presented in Fig. 5.3. Microemulsion droplets are negatively charged and reveal electrophoretic mobility, however, after applying an electrical current to the capillary, the buffer generate high electroosmotic flow (EOF) which overcomes the electrostatic force driving microemulsion droplets towards anode.

The partitioning of the solutes is based both on their electrokinetic mobility and hydrophobicity, allowing for efficient separation of both neutral and charged

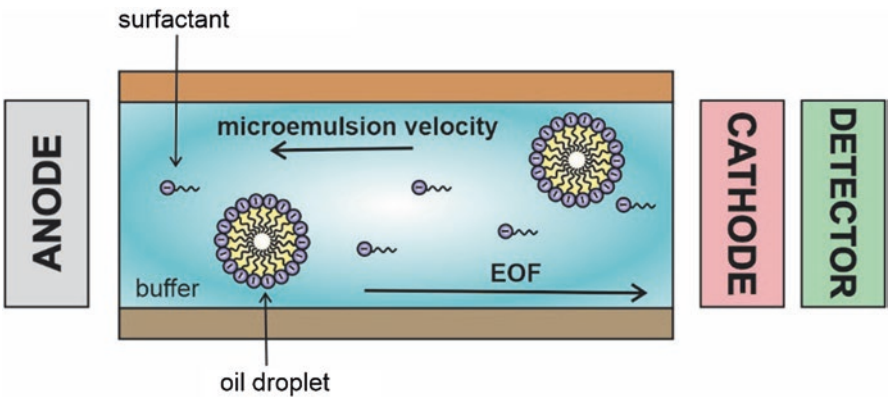

Fig. 5.3 The principle of MEEKC (Altria 2000); EOF – electroosmotic flow

molecules displaying different water affinity (Altria 2000; Altria et al. 2003). When a neutral compound is injected into the capillary, it will be partitioned between microemulsion droplets and buffer. Strongly hydrophobic analytes will reveal the tendency to dissolve in microemulsion droplets and migrate through the capillary with the same velocity. In such cases, long retention time is observed. Hydrophilic solutes are present mostly in the aqueous phase, revealing different retention time depending on their electrophoretic mobility and interaction with negatively charged droplets. It is noteworthy that negatively charged analytes will be repulsed by the droplets, while in the case of positively charged compounds ion pairing is observed. However, in both types of analytes, the diffusion into the hydrophobic core is prevented and the analyzed substance is present mostly at the hydrophilic site (Klampfl 2003).

5.3.4 Nanoparticle Formation

Microemulsions are frequently utilized as reaction media or templates for the preparation of various types of nanoparticles. In the case of inorganic nanoparticles, W/O microemulsion droplets may serve as containers for reagents. Mixing two different microemulsion systems containing separated substrates leads to droplets collisions and precipitation of the product. The synthesis of inorganic particles with the use of O/W microemulsions has also been described in the literature and the precursor might be either an ionic salt dissolved in water phase or an organometallic salt dissolved in oil phase (Magno et al. 2011; Housaindokht and Nakhaei Pour 2012; Kong et al. 2012; Sanchez-Dominguez et al. 2012). Microemulsions can be employed in the production of solid lipid nanoparticles (Müller et al. 2000; Shah et al. 2014; Chirio et al. 2019). In such cases, O/W systems obtained at the temperature above melting point of the lipid component are used. Finally, liquid droplets are transformed into solid lipid nanoparticles as a result of microemulsion dispersion in cold aqueous medium (Mehnert 2001).

Moreover, microemulsions can be used as reaction media for polymerization reactions of various types (Pavel 2004). The process performed for hydrophobic monomers incorporated in the internal phase of O/W microemulsions leads to the formation of polymer particles of various diameters, depending usually on the reaction conditions (He et al. 2003; Chen et al. 2010). In another approach, water-soluble monomers dissolved in W/O microemulsions are used (McAllister et al. 2002; Deng et al. 2003). The results of polymerization reaction performed with the use of bicontinuous systems (Peinado et al. 2006; Wang et al. 2017) were also reported and they depended mostly on the type of the applied monomers and the composition of microemulsions.

5.4 Antioxidants in Microemulsions

Taking into account the versatile and unique properties of microemulsions, including their excellent ability to dissolve substances of different polarities, they are frequently investigated as carrier systems for various active compounds. Very often microemulsions are considered as vehicles used in the development of novel pharmaceutical delivery systems (Talegaonkar et al. 2008) or cosmetics (Boonme 2007), but also as components of other biomedical devices (Malik et al. 2012). Most of the mentioned applications include liquid and semi-solid formulations for topical use (Froelich et al. 2017; Nastiti et al. 2017), as well as various oral dosage forms (Gibaud and Attivi 2012). For many years, another major area for microemulsions use has been the food industry.

Both in medical and food applications microemulsions are broadly investigated as carriers for antioxidant agents. It has been proven that in many cases, incorporation of such compounds into microemulsions may result in not only higher solubility and stability, but is followed by improved bioavailability, both after external application and ingestion. This in turn allows to obtain better effectiveness with lower concentrations of the actives.

The abundance of experimental data in literature clearly indicates multiple beneficial effects related to microemulsion-based systems for the delivery of antioxidants. The main targets posed to microemulsions include an improvement of skin anti-aging efficacy or anti-cancer activity, which are obtained due to the stability increase, deeper percutaneous penetration and stronger antioxidant effects. In terms of other administration routes, microemulsions can efficiently promote nose-to-brain transport. Several studies indicate that active ingredients incorporated in microemulsion-based media applied to the nasal mucous membrane can quickly reach the brain tissue and achieve higher concentrations compared to the conventional formulations (Shah et al. 2016). The described approach can also be useful to avoid systemic side effects frequently encountered after oral administration. The observed beneficial effects are related mostly to the direct transport from olfactory region in nasal cavity to central nervous system. In this way, the active ingredient bypasses the blood-brain barrier, the most important factor limiting the effectiveness of brain-targeted drug delivery (Alam et al. 2010; Lu et al. 2014).

In the case of natural products, when active ingredients are obtained from plant sources, microemulsions can also be used as excellent extraction media. Moreover, in some cases the protective action of microemulsions in preventing antioxidants from degradation was proven.

In the following paragraphs, the literature reports regarding the most frequently investigated antioxidant agents have been reviewed and discussed. It is noteworthy that all of the mentioned substances reveal poor solubility in water, which is challenging in terms of both technological process and absorption from gastrointestinal tract. The application of microemulsion as carrier or extraction medium is a simple and efficient method to overcome the potential difficulties related to low solubility and low absorption of active ingredients.

5.4.1 Carotenoids

Carotenoids are phytochemical dyes occurring abundantly in plant kingdom. Numerous scientific studies show the evidence for their preventive role in several chronic diseases related to the occurrence of an oxidative stress, like cancer and cardiovascular disorders (D'Odorico et al. 2000; Rao and Rao 2007; Riccioni 2009; Karppi et al. 2012; Jomova and Valko 2013; Kasperczyk et al. 2014). All carotenoids are lipophilic which might contribute to the formulation and processing difficulties encountered during extraction and obtaining stable carotenoid-loaded product.

β-Carotene is a one of the most frequently occurring plant carotenoids which displays antioxidant properties. It is present in large amounts in fresh fruits and vegetables, like carrots. Numerous scientific studies indicate its advantageous properties as a food component (Johnson and Krinsky 2009; Fiedor and Burda 2014; Woodside et al. 2015). These properties include chemopreventive potential, as well as the possibility to improve the efficiency of immune response and reduce the risk of coronary heart disease. Taking into consideration its beneficial properties and high concentration in plant sources, it is utilized as an alternative for synthetic food dyes. Depending on the localization and a physical form of β-carotene occurring in plants, the extraction might be more or less complicated. It was noted that the use of conventional methods involving organic solvents is usually related to the presence of toxic residues, which poses an important problem whenever food or pharmaceutical products are designed. Roohinejad et al. proposed the method for carotene extraction using O/W microemulsion as safe, efficient and cheap alternative to the conventional techniques employing relatively toxic organic solvents. In this method, in the first step pulsed electric field was applied to the carrot pomace to increase the efficiency of carotene extraction. Next, carrot pomace was freeze-dried to avoid water content changes in microemulsion used for extraction. Finally, the dried product was subjected to the extraction process using different times and temperatures and the impact of different variables was evaluated with the use of statistical methods. The obtained stable and transparent β-carotene-loaded microemulsion can be used as promising vehicle for fortification of transparent food, beverage and pharmaceutical products (Roohinejad et al. 2014b). The same authors in another report, prepared microemulsions containing β-carotene from carrot pomace and investigated their cytotoxicity toward Caco-2 cells. The microemulsions contained glycerol monocaprylocaprate (Capmul MCM), Tween® 80 and phosphate buffer. The idea was to check whether the carriers could protect the cells from damage in the presence of H_2O_2. It turned out that β-carotene concentration of 0.0313% gave bioprotection to the cells. The increase in cytotoxicity at the concentrations higher than 0.0313% was interpreted as the result of increasing Tween® 80 precipitation on the cell culture monolayer (Roohinejad et al. 2014a).

Chen & Zhong investigated the protective potential of microemulsion carrier with incorporated β-carotene against oxidation of the active ingredient. It was shown that the most important factor improving stability of the product was lecithin

content which might be related both to the properties of lecithin and to the increased viscosity of the system (Chen and Zhong 2015). Moreover, the increased content of lecithin (as a surfactant) contributed to better antioxidant performance of peppermint oil, which was applied as an oil phase. The analyzed formulations showed significantly increased thermal stability and resistance to ultraviolet (UV) radiation.

Chaari et al. presented the study related to carotenoids obtained from halophilic *Archaea* microorganisms. The aim of the project was to solubilize lipophilic compounds in micro- and nanoemulsions and to compare the stability and antioxidative potential of the obtained systems. It was shown that both investigated dispersions had similar radical-scavenging effects. However, microemulsion revealed better physical stability, which was obvious considering the thermodynamic and kinetic stabilities of both systems (Chaari et al. 2018). Another study focused on the stability of β-carotene and lemon oil-loaded microemulsion, in which the basic idea was to incorporate lipophilic flavors and coloring agents to transparent beverages with the use of microemulsion systems. The beverages obtained with the described microemulsions were physically stable and no phase separation was observed after 30 days. However, the color was not stable during storage which indicated oxidation of β-carotene (Calligaris et al. 2019).

Another extensively investigated carotenoid compound is lycopene, red compound present in tomatoes, watermelon and papaya. As an antioxidant, it reveals higher activity than β-carotene (Kelkel et al. 2011). It is noteworthy that the compound is poorly soluble in water and most food-grade oils, which is a cause of poor absorption of lycopene from the gastrointestinal tract. The mentioned effect contributed also to low bioavailability after oral administration. Therefore, the studies involving microemulsions as carriers usually aim at the solubilization of lycopene and improvement of biopharmaceutical properties (Spernath et al. 2002). Moreover, similarly to other carotenoids, alternative methods for lycopene extraction from plant sources are investigated.

According to Lopes et al., microemulsions can be used for topical supplementation of skin with antioxidants. The authors prepared two types of emulsions containing lycopene (0.05%, w/w). The formulations were composed of BRIJ-propylene glycol mixture (2:1, w/w) and different oil phases: mono/diglycerides of capric and caprylic acids or triglycerides of the same fatty acids. The aim was to increase lycopene penetration through the skin layers in order to obtain better protection against UV radiation. The experiments conducted on porcine ear skin showed that microemulsion-based solutions of the active compound revealed 6 to 3.6-fold greater penetration than a control solution (oil/propylene glycol). Moreover, significant effects of the increase of lycopene concentration in the skin were observed after addition of ascorbic acid to the formulations. The obtained microemulsions showed very low irritation tendency against skin cells (Lopes et al. 2010).

Pepe et al. presented another skin-related study performed with the use of lycopene-loaded microemulsion. In order to increase the antioxidant potential of the investigated topical formulation, they used ascorbic acid as another active ingredient. As an oil phase, monoglycerides of different chain lengths were applied. It was shown that the length of the lipophilic chain affected both water solubilization

capacity and skin permeation process. It was found that the shorter the monoglyceride hydrophobic chain, the higher water solubilization capacity of the obtained microemulsion. Regardless of the oil type, all lycopene-loaded microemulsions could significantly enhance the delivery of the active ingredient to viable skin layers and *stratum corneum*. However, the weakest effect was observed for the system with the lipid of intermediate chain length. The same system did not significantly enhance the delivery of ascorbic acid compared to the plain solution used as a reference. The enhancement effects observed for the monoglycerides with short and long chain for ascorbic acid were similar, while in the case of lycopene the systems with short chain monoglyceride performed better. It is noteworthy that lycopene was retained in the skin but did not cross it, which may indicate possible difficulties with transdermal delivery of this antioxidant (Pepe et al. 2012).

Guo et al. investigated microemulsion as a carrier improving bioavailability and brain targeting efficiency of orally administered lycopene. The pharmacokinetics and tissue distribution of lycopene were tested with the use of animal model with lycopene dissolved in olive oil as a reference formulation. It was shown that the microemulsion-based system significantly increased absorption of the active ingredient from gastrointestinal tract. Moreover, after oral administration of microemulsion-based medium, higher amounts of lycopene were found in the brain tissue when compared to the simple solution. Several different hypotheses explaining the possible impact of microemulsion on blood-brain barrier were presented. The obtained results are particularly important for the research exploring novel therapeutic approaches in neurodegenerative disorders (Guo et al. 2019).

Application of microemulsion technique to extract lycopene from tomato pomace (considered as a waste) was investigated in some studies. The obtained results allowed simple and safe recovery of lycopene from tomato pomace (and possibly from tomato industrial wastes). The recovery value reached up to 35% in the case of the best formulation by using saponin as a natural surfactant and combined ultrasonic and enzymatic pretreatment (Amiri-Rigi and Abbasi 2016). The same authors studied the feasibility of microemulsion technique in enhancing the solubility of lycopene, which could lead to an efficient extraction from tomato pomace. The obtained lycopene-loaded microemulsions were analyzed for the stability during several technological processes, such as pasteurization, sterilization, freezing and UV-irradiation. It was shown that the investigated systems were not affected by the applied procedures as long as the temperature and time were controlled (Amiri-Rigi and Abbasi 2017). The same research group presented the results obtained for the food-grade microemulsion composed of different proportions of olive oil, lecithin, 1-propanol and water applied as an extraction medium for retrieving lycopen from tomato pomace. After four cycles of extraction with the optimized microemulsion, the maximum extraction efficiency of 88% was obtained. It is noteworthy that the applied medium contained mostly biocompatible components and can be used as an interesting alternative for toxic organic solvents (Amiri-Rigi and Abbasi 2019).

5.4.2 Curcumin

Curcumin is a yellow polyphenol compound occurring in *Curcuma longa* rhizome, which is popularly used as a spice and food colorant. It is well known mostly for its antioxidant and anticancer properties (Parvathy et al. 2009) but reveals also beneficial effects in inflammatory (Mobasheri et al. 2012), neurological (Cole et al. 2007) and infectious (Padmanaban and Rangarajan 2016) conditions. Even though the antioxidant activity of curcumin has been proven in numerous scientific studies, the exact mechanism of this phenomenon remains unclear and several different hypotheses have been proposed, including free radical scavenging effects and preventive effects in lipid peroxidation (Galano et al. 2009). One of the most important difficulties encountered in the curcumin delivery is its low water solubility affecting its bioavailability. In order to achieve therapeutic plasma concentrations, extremely high oral doses of curcumin are required. The ingestion of high amounts of the active ingredient is not comfortable for the patients and also results in an increased risk of side effects (Yen et al. 2010). Another important disadvantage of curcumin is its susceptibility to photo-degradation and hydrolysis in alkaline conditions (Tønnesen et al. 2002). Microemulsions applied as carriers dissolve high amounts of this active ingredient, as well as improve its bioavailability. Bergonzi et al. designed and evaluated microemulsion as a medium for dissolution and oral administration of curcumin. The solubility of the active ingredient depended on the composition of micremulsion, however, in the case of all investigated formulations significant improvement with respect to aqueous environment was observed. The obtained microemulsions were physically stable and remained transparent for two months. Moreover, the dilution tests indicate that they would not transform into coarse emulsions after oral administration (Bergonzi et al. 2014).

Hu et al. also designed and evaluated curcumin-loaded microemulsions for potential oral administration. Based on the solubility screening, the optimal formulation was composed of Capryol™ 90 (oil phase) Cremophor® RH40 (surfactant), Transcutol® P (co-surfactant) and water. The plasma concentration levels observed with the use of animal model indicate that microemulsions can be utilized as drug delivery systems for the active ingredients revealing poor water solubility and poor bioavailability. The obtained results were significantly better when compared to oral suspension. The authors suggest that the presented system might be potentially useful in the production of nutraceuticals and functional food (Hu et al. 2012). Similar bioavailability improvement was reported by Xiao et al. based on the study performed on the mixture of three different curcuminoids incorporated in microemulsion (Xiao et al. 2013).

In addition, microemulsions have been investigated as systems for delivering curcumin through other routes (nasal, skin, etc.). For example, Liu et al. showed that microemulsions can be used as carriers for antioxidants in photodynamic treatment of localized bacterial inflammations. The authors prepared microemulsions using distilled water, geraniol oil, propylene glycol, and Tween® 80. Curcumin (4000 ppm) was used as a photoactive agent. The overall idea was to increase the solubility of

curcumin due to improve the photodynamic effects toward *Pseudomonas aeruginosa* colonies. Blue light-emitting diode (455 nm) was used for activation of curcumin and further generation of singlet oxygen. It was clearly shown that microemulsions increased photoinactivation of *P. aeruginosa* both in the planktonic and biofilm form. Moreover, ex vivo experiments on neonatal porcine ear skin revealed that microemulsions decreased the penetration of curcumin in comparison to aqueous solutions. The effect was significant regarding potential application on patients' skin and limited possible damage to healthy tissue (Liu et al. 2016).

Mandal et al. designed mucoadhesive microemulsion for intranasal delivery of curcumin. The aim was to increase the brain uptake of the compound. According to the drug (curcumin) solubility, Capmul® MCM, a mono-diglyceride of caprylic and capric acids, was selected as the oil phase and polycarbophil as mucoadhesive polymer was added to the formulations as well. The in vivo experiments on male albino rats showed that following intranasal administration, brain concentrations of the compound were higher than after an intravenous injection. Moreover, no damage of the nasal mucosa was observed (Mandal et al. 2016).

Ghosh et al. presented an interesting study on the physiochemical properties of curcumin-loaded microemulsions containing gold and silver nanoparticles with the aim of checking the possible impact of metal nanoparticles on photochemical properties and antioxidant performance of curcumin. The study revealed that curcumin formed conjugates with silver nanoparticles and consequently the excited state lifetime of the active ingredient increased. In the case of the system with gold nanoparticles, the opposite effect was observed. The excited state lifetime of curcumin was decreased which was explained with possible nanometal surface energy transfer (NSET). The observed phenomenon was a result of the overlap between emission and absorption spectra of curcumin and gold nanoparticles, respectively. In the investigated system, curcumin acted as the fluorophore donor while gold was the acceptor. The results obtained for both systems can be useful in bioimaging applications (Ghosh et al. 2020).

5.4.3 Flavonoids

Flavonoids are wide group of phytochemical compounds occurring abundantly in plants. Considering their chemical structure, they are categorized into several different classes including flavonols, anthocyanins, isoflavones, flavanones, proanthocyanidins and flavones (Brodowska 2017). It was shown that their presence in daily diet is beneficial in many different health aspects, for example they are efficient scavengers for reactive oxygen species (Terao 2009). This effect is important in prevention of cancer and complication of many chronic diseases, like diabetes and cardiovascular problems (Le Marchand 2002). Flavonoids reveal good thermal stability making them resistant to the conditions applied during industrial processing. The most important problem encountered in flavonoids delivery is their poor and highly variable bioavailability depending on their molecular weight, glycosylation

and esterification (Thilakarathna and Rupasinghe 2013). It was found that small molecular weight polyphenols, like caffeic acid, can be easily absorbed from the gastrointestinal tract, while large proanthocyanidins, which are in fact flavonoid polymers, reveal poor bioavailability. Another important factor is the type of sugar moiety bonded to the aglycone. It was found that glucoside derivative of quercetin revealed better intestinal absorption than the aglycone and corresponding rhamnoside derivatives (Scalbert et al. 2002). Incorporation of flavonoids in different carriers, such as liposomes (Kerdudo et al. 2014), nanoparticles (Roussaki et al. 2014) or microemulsions is one of the most commonly applied methods to increase the bioavailability of different classes of these compounds. It is important to notice that the applied carrier might have an impact directly on the antioxidant activity of the incorporated agent. Fan et al. revealed that propolis flavone had higher in vivo antioxidant activity in microemulsion than when administrating alone (Fan et al. 2014). Among the most frequently investigated antioxidant flavonoids incorporated in microemulsions quercetin, resveratrol and its derivatives, hesperitin and catechins should be mentioned.

5.4.3.1 Quercetin

Quercetin is a very popular plant flavonol. It can be found in numerous different edible plants, however, the highest amounts of quercetin are observed in onion. It occurs in a form of different glycosides, including the most popular rutin (3-rhamnoglucoside), galactosides, arabinosides and glucosides present in onion (Erlund 2004). Quercetin glycosides reveal hydrophilic properties, therefore, initially it was expected that only non-glycosylated form could be absorbed from gastrointestinal tract. However, the studies comparing different forms of quercetin indicate that the presence of sugar moiety significantly improves bioavailability which might be related either to deglycosylation or carrier-mediated transport (Boots et al. 2008). Poor water solubility and instability of quercetin seem to be the most important problems in its oral and topical delivery. Therefore, several different technologies have been investigated in order to overcome these difficulties, including incorporation in microemulsion (Nagula and Wairkar 2019). Skin penetration of quercetin from microemulsions was investigated by Kitagawa et al. They prepared quercetin-loaded microemulsions composed of isopropyl myristate, 150 mM NaCl solution, Tween® 80 and ethanol. It was observed that intradermal delivery of the active compound from microemulsion vehicle was more efficient than from unmixed organic solvents. The authors supported the theory that the effect was related to microemulsion breakage upon contact with skin followed by quercetin release from the interface region. Another possibility is that microemulsion partly mixes with *stratum corneum* lipids and therefore enhances the permeation of the drug. The authors stated that continuous and spontaneous fluctuations of microemulsions interfaces contributed to high drug mobility and thus enhanced the drug diffusion

process (Kitagawa et al. 2009). Quercetin-loaded microemulsions for topical use were also prepared by Kajbafvala et al. It was observed that the skin retention decreased with increasing surfactant/co-surfactant ratio, which was related to increasing droplet size. The authors have proven that in vitro quercetin release directly depended on surfactant concentration (Kajbafvala et al. 2018).

In another work, the influence of the storage conditions (temperature, humidity, light) on physical, chemical and functional stability of the quercetin-loaded microemulsions was investigated. As a result, they were physically stable; however, some chemical and functional changes occurred indicating the necessity of special storage conditions. Promising results were obtained when the samples were exposed to UV-B radiation and it was shown that the microemulsions can be used as protective agents against radiation skin damage (Vicentini et al. 2011).

Another study devoted to design quercetin-loaded microemulsion to improve solubility and bioavailability of the active ingredient was presented by Gao et al. To obtain the final microemulsion composition, simplex lattice experiment design was employed. Quercetin absorption after oral administration was evaluated with the use of rat model with micellar solution applied as a reference. The recorded differences were statistically significant and indicated faster absorption from the intestine and prolonged presence in the plasma in the case of microemulsion-based carrier. The observed effect was assigned to absorption enhancing effect exerted by lipid on the lymphatic route (Gao et al. 2009).

Censi et al. indicated the difficulties frequently encountered in obtaining therapeutic concentrations of quercetin in systemic circulation after transdermal delivery. They mentioned that problems with poor absorption of the active ingredient could be overcome with the use of properly selected permeation enhancers, like Transcutol® P. It is noteworthy that in microemulsions, this component might act as a solubilizer for the active component and co-surfactant, which enables the formation of microemulsion due to its ability to decrease interfacial tension. Moreover, it is widely known as a valuable skin permeation enhancer. Quercetin-loaded microemulsion in this study was evaluated using excised pig skin model. The obtained results were compared to those recorded for corresponding Transcutol® P solution, oil/water/surfactant solution and oil/Transcutol® P/surfactant solutions and it was found out that solubilizing agent had a significant impact on quercetin absorption. The highest permeation rate was observed for simple Transcutol® P solution while the system without it (i.e. oil/water/surfactant solution), had the lowest rate. Quercetin-based microemulsion revealed better properties than the formulations without solubilizer and without water. It is also important to note that in the case of the systems that improve permeation through the skin, lower amounts of quercetin were accumulated in skin (Censi et al. 2012).

Microemulsions can be considered as carriers to improve the stability of quercetin. Lv et al. obtained essential oil-based systems to improve water solubility of quercetin and to reduce its sensitivity to light and pH instability. The active ingredient was significantly more resistant to alkaline pH and UV radiation (Lv et al. 2017).

5.4.3.2 Resveratrol

Resveratrol is a polyphenolic component of grapes, berries and other plants. It is commonly known as a compound related to so called "French paradox" describing low prevalence of cardiovascular disease among French population, despite saturated lipid-rich diet. The explanation of this phenomenon was based on the data on high consumption of red wine, which is a good source of resveratrol. Its antioxidant properties are related not only to its free radicals scavenging activity but also to an ability to induce the expression of specific enzymes revealing antioxidant activity (Smoliga et al. 2011). Similar to other flavonoids, resveratrol reveals low bioavailability, even though its absorption from gastrointestinal tract reaches about 75% (Pangeni et al. 2014). It was shown that this phenomenon is related mostly to its rapid transformation to sulfate and glucuronide metabolites (Walle et al. 2004). Another important disadvantage of resveratrol is its poor solubility in water. Therefore, numerous technological approaches aiming at reduction of the mentioned effects have been investigated. Most of the studies proposed its incorporation into liposomes, micro- and nanocapsules and nanoparticles as efficient platforms to overcome the described difficulties (Augustin et al. 2013). Microemulsions due to their ability to improve dermal absorption of active ingredients are considered as potential carriers in transdermal resveratrol delivery. Sucrose fatty acid ester microemulsions were designed by Yutani et al. with the aim of promoting skin delivery of resveratrol. In vitro intradermal and transdermal experiments on Yukatan micropig skin revealed that sucrose oleate had the best performance among the other sucrose esters (laurate, myristate, palmitate, stearate). The authors stated that resveratrol skin incorporation efficiency was approximately inversely proportional to its concentration (Yutani et al. 2016). In another study, Das et al. investigated microemulsion-based gels containing tea tree oil and medium chain glyceride as carriers for resveratrol (Das et al. 2020). The obtained systems were tested for drug release and permeation with the use of polysulfone and Strat-M™ synthetic membranes, respectively. Strat-M™ is usually applied as an alternative to human or animal skin ex vivo model. The obtained results indicate that the active ingredient permeated through the membrane in relatively small amounts and in a prolonged manner, which is favorable in cosmetic applications.

For oral administration route, self-emulsifying drug delivery systems (SEDDS) are considered as potential carriers for resveratrol delivery. For instance, Chen et al. incorporated resveratrol into a SEDDS with purpose of improving its absorption after oral administration. The formulations were composed of ethyl oleate, Tween® 80 and polyethylene glycol (PEG) 400 as the oil, surfactant and co-surfactant, respectively. The drug concentration was 5%. The formulation revealed stronger antioxidant activity and was less toxic to cells than free resveratrol. The results were very promising in terms of food supplementation with the active ingredient (Chen et al. 2015).

In a study performed by Bolko et al., resveratrol was incorporated in an innovative mixed lipid phase SMEDDS with the aim of enhancing its solubility. The mixed lipid phase was composed of long-chained triglyceride plus medium chain

mono- and diglycerides and it showed the best self-emulsifying ability in terms of self-emulsifying time as well as droplet size and monodispersity of microemulsions achieved upon SMEDDS dilution with aqueous phase. This formulation also displayed higher drug release rate in comparison to the corresponding system containing single lipid in an oil phase (Bolko et al. 2014). The same research group using Caco-2 model showed that the applied formulation had high drug loading capacity and the incorporated active ingredient was released rapidly and did not impair the viability of in vitro cell cultures. Moreover, it was shown that the applied excipients might reduce the efflux of resveratrol metabolites which can contribute also to the reduction of intestinal metabolism and improvement of bioavailability (Seljak et al. 2014). Finally, in another report about incorporation of resveratrol in SMEDDS, it was shown that the solubility of the active ingredient in self-microemulsifying carrier was about 1000 times higher than its solubility in water. On the other hand, the authors obtained satisfactory results in in vitro drug release tests, showing that the process was faster in the case of encapsulated antioxidant than for resveratrol powder. Moreover, the concentrations of the drug observed in the receptor fluids were not depended on pH value of media (Tang et al. 2019).

5.4.3.3 Other Flavonoids

Apart from the two most extensively studied antioxidant flavonoids (quercetin and resveratrol), there are several studies describing other compounds with related structure. For example, hesperetin-loaded microemulsion for topical use was designed by Tsai et al., which revealed better in vitro permeation in comparison to the aqueous and isopropyl myristate suspension dosage form of hesperetin. Studies on the influence of co-surfactant on the drug permeation capacity showed that propylene glycol yielded the highest permeation rate, followed by ethanol, glycerol and PEG 400. The permeation also depended on HLB of co-surfactants. The analyzed microemulsion demostrated very good whitening effects on skin (Tsai et al. 2010).

Solubility of apigenin, a bioactive flavonoid with various pharmacological activities was improved by incorporating apigenin/hydroxypropyl-β-cyclodextrin complex into microemulsions. No co-surfactant was used for preparation of the investigated system. In vitro drug release profile obtained with the use of dialysis technique indicated zero-order kinetic process at the whole range of measurement. The authors concluded that the aqueous solubility of apigenin remarkably increased in the complex with Tween® 80 based O/W microemulsions, via solubilizing in the palisade layer, the inner oil core, and outer water phase (Zhao et al. 2016). The same authors presented another related study in which apigenin was encapsulated in complex system composed of O/W microemulsion thickened with gellan gum. The apigenin release was studied under different pH conditions. The observed results indicated two different release mechanisms depending on the pH of receptor media. At pH = 1.2 corresponding to the stomach environment, the active ingredient was released in a diffusion-controlled manner, while at pH = 7.4 similar to the duodenal conditions, the process was controlled by erosion (Zhao and Wang 2019).

5.4.4 Vitamin E

The term "vitamin E" in fact comprises a group of tocopherols and tocotrienols. Both forms are structurally similar but tocotrienols contain three double bonds in the side chain instead of two. Among all naturally occurring and synthetic tocopherols and tocotrienols, α-tocopherol reveals the highest biological activity. The most important function of vitamin E is its free radical-scavenging ability protecting biological macromolecules from damage. Vitamin E is lipophilic and occupies cell membranes and protects membrane lipids from oxidation (Dutta and Dutta 2003; Traber and Atkinson 2007). As a hydrophobic compound, it is poorly soluble in water and its absorption from gastrointestinal tract is closely related to lipid absorption (Rigotti 2007). Similar to other hydrophobic active ingredients, efficient uptake and delivery of vitamin E can be challenging. Therefore, in the studies focusing on the delivery of this compound, usually lipid-based carriers, including microemulsions, are applied. Another beneficial effect of vitamin E incorporation as an excipient is reduction of gastrointestinal side effects that can be observed after oral administration of microemulsions (Gibaud and Attivi 2012).

With the purpose of improving the bioavailability of vitamin E, it was encapsulated in microemulsion system and its antinociceptive, antioxidant, antidepressant- and anxiolytic-like activities in mice were evaluated. It was shown that α-tocopherol incorporated in microemulsion could protect lipids from peroxidation more efficiently comparing to free vitamin E. The observed results suggest that oxidative stress may be involved in the mechanism of some neurological disorders and vitamin E-loaded microemulsion has tremendous potential for the treatment of these conditions (Wilhelm et al. 2018). Carvalho et al. presented a study involving microemulsions as carriers for dermal delivery of vitamin E and other compounds. Microemulsions were applied in order to overcome technological challenges related to obtaining stable and effective formulation with poorly water-soluble drugs. It was shown that depending on the lipophilicity of the incorporated active ingredient, the applied approach could allow for more efficient dermal topical delivery of the drug (Carvalho et al. 2017).

Co-delivery of two synergistically acting antioxidant agents is useful for topical skin protection and treatment. For example, in a study presented by Cichewicz et al., microemulsions were used to promote the concomitant delivery of α-tocopherol and lipoic acid into viable skin layers. Microemulsions with different water content and droplet charge were investigated. It was shown that the structural features of the carrier affected the cutaneous delivery of α-tocopherol. However, the same factors had no impact on lipoic acid. The authors concluded that combination of these two antioxidants could potentially protect skin against damage associated with the generation of reactive oxygen species (Cichewicz et al. 2013). Similarly, Praça et al. investigated vitamins A and E-loaded W/O microemulsions for potential dermal application. The obtained system was physically stable and in vivo treatments showed reduced dermal expression of tumor necrosis factor alpha (TNF)-α by 1.3-fold ($p < 0.01$), when compared to unloaded microemulsion treatment group (Praça et al. 2020).

5.5 Summary

Antioxidants are wide and diverse group of compounds revealing different physicochemical properties. Nevertheless, there are few features, which seem to be commonly described as challenges in the studies focusing on antioxidant technological and delivery issues. Most of the described compounds reveal poor water solubility that causes difficulties both in extraction from plant sources and in the delivery as active pharmaceutical ingredients. It is noteworthy that in the case of such compounds bioavailability is usually low after oral administration, which also limits the possibility to achieve the therapeutic effect. Therefore, the selection of proper carrier enabling dissolution of active ingredient may be crucial for achieving the main goal of applying antioxidants. On the other hand, the efficient extraction process also requires the selection of proper medium revealing good solubilizing properties. Microemulsions that contain several different solubilizing agents seem to be perfect carriers and extraction liquids for the compounds revealing low solubility in water. Moreover, numerous studies confirm their ability to increase the absorption of the therapeutic agent from skin or gastrointestinal tract, which contributes to better efficacy of the applied formulation too. In the case of antioxidants which are often susceptible to degradation, a proper carrier may also improve the stability of the main ingredient and decrease its sensitivity to light and oxygen, as was proven for quercetin-loaded microemulsions (Lv et al. 2017).

Despite numerous advantages of microemulsions in antioxidant technology, it must be kept in mind that they are not free from drawbacks. One of the most important ones is the presence of surfactants and co-surfactants, which may act as irritants both applied topically and in gastrointestinal tract. The side effects related to skin irritation, impairing the barrier function of *stratum corneum* and dehydration were already described in the literature (Lehmann et al. 2001). Similar issues have been observed for self-microemulsifying systems administered orally (Gursoy and Benita 2004). It is also noteworthy that the components responsible for skin and mucous membrane irritation are necessary for microemulsion formation and usually occur in such systems at high concentrations, which increase the risk of side effects occurrence.

References

Alam MI, Beg S, Samad A et al (2010) Strategy for effective brain drug delivery. Eur J Pharm Sci 40:385–403. https://doi.org/10.1016/j.ejps.2010.05.003

Aliberti ALM, de Queiroz AC, Praça FSG et al (2017) Ketoprofen microemulsion for improved skin delivery and in vivo anti-inflammatory effect. AAPS PharmSciTech 18:2783–2791. https://doi.org/10.1208/s12249-017-0749-6

Altria KD (2000) Background theory and applications of microemulsion electrokinetic chromatography. J Chromatogr A 892:171–186. https://doi.org/10.1016/S0021-9673(00)00088-1

Altria KD, Mahuzier P-E, Clark BJ (2003) Background and operating parameters in microemulsion electrokinetic chromatography. Electrophoresis 24:315–324. https://doi.org/10.1002/elps.200390041

Amiri-Rigi A, Abbasi S (2016) Microemulsion-based lycopene extraction: effect of surfactants, co-surfactants and pretreatments. Food Chem 197:1002–1007. https://doi.org/10.1016/j.foodchem.2015.11.077

Amiri-Rigi A, Abbasi S (2017) Stability assessment of lycopene microemulsion prepared using tomato industrial waste against various processing conditions. J Sci Food Agric 97:4922–4928. https://doi.org/10.1002/jsfa.8368

Amiri-Rigi A, Abbasi S (2019) Extraction of lycopene using a lecithin-based olive oil microemulsion. Food Chem 272:568–573. https://doi.org/10.1016/j.foodchem.2018.08.080

Anton N, Vandamme TF (2011) Nano-emulsions and micro-emulsions: clarifications of the critical differences. Pharm Res 28:978–985. https://doi.org/10.1007/s11095-010-0309-1

Augustin MA, Sanguansri L, Lockett T (2013) Nano- and micro-encapsulated systems for enhancing the delivery of resveratrol. Ann N Y Acad Sci 1290:107–112. https://doi.org/10.1111/nyas.12130

Bera A, Mandal A (2015) Microemulsions: a novel approach to enhanced oil recovery: a review. J Pet Explor Prod Technol 5:255–268. https://doi.org/10.1007/s13202-014-0139-5

Bergonzi MC, Hamdouch R, Mazzacuva F et al (2014) Optimization, characterization and invitro evaluation of curcumin microemulsions. LWT – Food Sci Technol 59:148–155. https://doi.org/10.1016/j.lwt.2014.06.009

Bolko K, Zvonar A, Gašperlin M (2014) Mixed lipid phase SMEDDS as an innovative approach to enhance resveratrol solubility. Drug Dev Ind Pharm 40:102–109. https://doi.org/10.3109/03639045.2012.749888

Boonme P (2007) Applications of microemulsions in cosmetics. J Cosmet Dermatol 6:223–228. https://doi.org/10.1111/j.1473-2165.2007.00337.x

Boots AW, Haenen GRMM, Bast A (2008) Health effects of quercetin: from antioxidant to nutraceutical. Eur J Pharmacol 585:325–337. https://doi.org/10.1016/j.ejphar.2008.03.008

Brodowska K (2017) Natural flavonoids: classification, potential role, and application of flavonoid analogues. Eur J Biol Res 7:108–123. https://doi.org/10.5281/zenodo.545778

Callender SP, Mathews JA, Kobernyk K, Wettig SD (2017) Microemulsion utility in pharmaceuticals: implications for multi-drug delivery. Int J Pharm 526:425–442. https://doi.org/10.1016/j.ijpharm.2017.05.005

Calligaris S, Manzocco L, Valoppi F et al (2019) Microemulsions as delivery systems of lemon oil and β-carotene into beverages: stability test under different light conditions. J Sci Food Agric 99:7016–7020. https://doi.org/10.1002/jsfa.9973

Carvalho VF, de Lemos DP, Vieira CS et al (2017) Potential of non-aqueous microemulsions to improve the delivery of lipophilic drugs to the skin. AAPS PharmSciTech 18:1739–1749. https://doi.org/10.1208/s12249-016-0643-7

Censi R, Martena V, Hoti E et al (2012) Permeation and skin retention of quercetin from microemulsions containing Transcutol ® P. Drug Dev Ind Pharm 38:1128–1133. https://doi.org/10.3109/03639045.2011.641564

Chaari M, Theochari I, Papadimitriou V et al (2018) Encapsulation of carotenoids extracted from halophilic Archaea in oil-in-water (O/W) micro- and nano-emulsions. Colloids Surf B Biointerfaces 161:219–227. https://doi.org/10.1016/j.colsurfb.2017.10.042

Chen H, Zhong Q (2015) Thermal and UV stability of β-carotene dissolved in peppermint oil microemulsified by sunflower lecithin and Tween 20 blend. Food Chem 174:630–636. https://doi.org/10.1016/j.foodchem.2014.11.116

Chen W, Liu X, Liu Y et al (2010) Synthesis of PMMA and PMMA/PS nanoparticles by microemulsion polymerization with a new vapor monomer feeding system. Colloids Surf A Physicochem Eng Asp 364:145–150. https://doi.org/10.1016/j.colsurfa.2010.05.010

Chen Y, Zhang H, Yang J, Sun H (2015) Improved antioxidant capacity of optimization of a self-microemulsifying drug delivery system for resveratrol. Molecules 20:21167–21177. https://doi.org/10.3390/molecules201219750

Chirio D, Peira E, Dianzani C et al (2019) Development of solid lipid nanoparticles by cold dilution of microemulsions: curcumin loading, preliminary in vitro studies, and biodistribution. Nano 9:247. https://doi.org/10.3390/nano9020230

Cichewicz A, Pacleb C, Connors A et al (2013) Cutaneous delivery of α-tocopherol and lipoic acid using microemulsions: influence of composition and charge. J Pharm Pharmacol 65:817–826. https://doi.org/10.1111/jphp.12045

Cole GM, Teter B, Frautschy SA (2007) Neuroprotective effects of curcumin. In: Advances in experimental medicine and biology. Springer, New York, pp 197–212

Constantinides PP (1995) Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. Pharm Res Off J Am Assoc Pharm Sci 12:1561–1572. https://doi.org/10.1023/A:1016268311867

D'Odorico A, Martines D, Kiechl S et al (2000) High plasma levels of α- and β-carotene are associated with a lower risk of atherosclerosisResults from the Bruneck study. Atherosclerosis 153:231–239. https://doi.org/10.1016/S0021-9150(00)00403-2

Danielsson I, Lindman B (1981) The definition of microemulsion. Colloids Surf 3:391–392. https://doi.org/10.1016/0166-6622(81)80064-9

Das S, Lee SH, Chow PS, Macbeath C (2020) Microemulsion composed of combination of skin beneficial oils as vehicle: development of resveratrol-loaded microemulsion based formulations for skin care applications. Colloids Surf B Biointerfaces 194:111161. https://doi.org/10.1016/j.colsurfb.2020.111161

Deng Y, Wang L, Yang W et al (2003) Preparation of magnetic polymeric particles via inverse microemulsion polymerization process. J Magn Magn Mater 257:69–78. https://doi.org/10.1016/S0304-8853(02)00987-3

Djordjevic L, Primorac M, Stupar M, Krajisnik D (2004) Characterization of caprylocaproyl macrogolglycerides based microemulsion drug delivery vehicles for an amphiphilic drug. Int J Pharm 271:11–19. https://doi.org/10.1016/j.ijpharm.2003.10.037

Dutta A, Dutta SK (2003) Vitamin e and its role in the prevention of atherosclerosis and carcinogenesis: a review. J Am Coll Nutr 22:258–268. https://doi.org/10.1080/07315724.2003.10719302

Erlund I (2004) Review of the flavonoids quercetin, hesperetin, and naringenin. Dietary sources, bioactivities, bioavailability, and epidemiology. Nutr Res 24:851–874. https://doi.org/10.1016/j.nutres.2004.07.005

Fan Y, Ma L, Zhang W et al (2014) The design of propolis flavone microemulsion and its effect on enhancing the immunity and antioxidant activity in mice. Int J Biol Macromol 65:200–207. https://doi.org/10.1016/j.ijbiomac.2014.01.041

Fanun M (ed) (2008) Microemulsions. Properties and applications, 1st edn. CRC Press, Boca Raton

Fiedor J, Burda K (2014) Potential role of carotenoids as antioxidants in human health and disease. Nutrients 6:466–488. https://doi.org/10.3390/nu6020466

Froelich A, Osmałek T, Snela A et al (2017) Novel microemulsion-based gels for topical delivery of indomethacin: formulation, physicochemical properties and in vitro drug release studies. J Colloid Interface Sci 507:323–336. https://doi.org/10.1016/j.jcis.2017.08.011

Galano A, Álvarez-Diduk R, Ramírez-Silva MT et al (2009) Role of the reacting free radicals on the antioxidant mechanism of curcumin. Chem Phys 363:13–23. https://doi.org/10.1016/j.chemphys.2009.07.003

Gannu R, Palem CR, Yamsani VV et al (2010) Enhanced bioavailability of lacidipine via microemulsion based transdermal gels: formulation optimization, ex vivo and in vivo characterization. Int J Pharm 388:231–241. https://doi.org/10.1016/j.ijpharm.2009.12.050

Gao Y, Wang Y, Ma Y et al (2009) Formulation optimization and in situ absorption in rat intestinal tract of quercetin-loaded microemulsion. Colloids Surf B Biointerfaces 71:306–314. https://doi.org/10.1016/j.colsurfb.2009.03.005

Ghosh M, Kundu S, Pyne A, Sarkar N (2020) Unveiling the behavior of curcumin in biocompatible microemulsion and its differential interaction with gold and silver nanoparticles. J Phys Chem C 124:3905–3914. https://doi.org/10.1021/acs.jpcc.9b11553

Ghouas H, Haddou B, Kameche M et al (2016) Removal of tannic acid from aqueous solution by cloud point extraction and investigation of surfactant regeneration by microemulsion extraction. J Surfactant Deterg 19:57–66. https://doi.org/10.1007/s11743-015-1764-9

Gibaud S, Attivi D (2012) Microemulsions for oral administration and their therapeutic applications. Expert Opin Drug Deliv 9:937–951. https://doi.org/10.1517/17425247.2012.694865

Guo Y, Mao X, Zhang J et al (2019) Oral delivery of lycopene-loaded microemulsion for brain-targeting: preparation, characterization, pharmacokinetic evaluation and tissue distribution. Drug Deliv 26:1191–1205. https://doi.org/10.1080/10717544.2019.1689312

Gursoy RN, Benita S (2004) Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacother 58:173–182. https://doi.org/10.1016/j.biopha.2004.02.001

He G, Pan Q, Rempel GL (2003) Synthesis of poly(methyl methacrylate) nanosize particles by differential microemulsion polymerization. Macromol Rapid Commun 24:585–588. https://doi.org/10.1002/marc.200390089

He CX, He ZG, Gao JQ (2010) Microemulsions as drug delivery systems to improve the solubility and the bioavailability of poorly water-soluble drugs. Expert Opin Drug Deliv 7:445–460. https://doi.org/10.1517/17425241003596337

Hoar TP, Schulman JH (1943) Transparent water-in-oil dispersions: the oleopathic hydro-micelle. Nature 152:102–103. https://doi.org/10.1038/152102a0

Housaindokht MR, Nakhaei Pour A (2012) Study the effect of HLB of surfactant on particle size distribution of hematite nanoparticles prepared via the reverse microemulsion. Solid State Sci 14:622–625. https://doi.org/10.1016/j.solidstatesciences.2012.01.016

Hu L, Jia Y, Niu F et al (2012) Preparation and enhancement of oral bioavailability of curcumin using microemulsions vehicle. J Agric Food Chem 60:7137–7141. https://doi.org/10.1021/jf204078t

Johnson EJ, Krinsky NI (2009) Carotenoids and coronary heart disease. In: Carotenoids. Birkhäuser, Basel, pp 287–300

Jomova K, Valko M (2013) Health protective effects of carotenoids and their interactions with other biological antioxidants. Eur J Med Chem 70:102–110. https://doi.org/10.1016/j.ejmech.2013.09.054

Kajbafvala A, Salabat A, Salimi A (2018) Formulation, characterization, and in vitro/ex vivo evaluation of quercetin-loaded microemulsion for topical application. Pharm Dev Technol 23:741–750. https://doi.org/10.1080/10837450.2016.1263995

Karppi J, Laukkanen JA, Mäkikallio TH et al (2012) Low β-carotene concentrations increase the risk of cardiovascular disease mortality among Finnish men with risk factors. Nutr Metab Cardiovasc Dis 22:921–928. https://doi.org/10.1016/j.numecd.2012.01.008

Kasperczyk S, Dobrakowski M, Kasperczyk J et al (2014) Beta-carotene reduces oxidative stress, improves glutathione metabolism and modifies antioxidant defense systems in lead-exposed workers. Toxicol Appl Pharmacol 280:36–41. https://doi.org/10.1016/j.taap.2014.07.006

Kelkel M, Schumacher M, Dicato M, Diederich M (2011) Antioxidant and anti-proliferative properties of lycopene. Free Radic Res 45(8):925–940

Kerdudo A, Dingas A, Fernandez X, Faure C (2014) Encapsulation of rutin and naringenin in multilamellar vesicles for optimum antioxidant activity. Food Chem 159:12–19. https://doi.org/10.1016/j.foodchem.2014.03.005

Kitagawa S, Tanaka Y, Tanaka M et al (2009) Enhanced skin delivery of quercetin by microemulsion. J Pharm Pharmacol 61:855–860. https://doi.org/10.1211/jpp.61.07.0003

Klampfl CW (2003) Solvent effects in microemulsion electrokinetic chromatography. Electrophoresis 24:1537–1543. https://doi.org/10.1002/elps.200305379

Kogan A, Garti N (2006) Microemulsions as transdermal drug delivery vehicles. Adv Colloid Interf Sci 123–126:369–385. https://doi.org/10.1016/j.cis.2006.05.014

Kohli K, Chopra S, Dhar D et al (2010) Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability. Drug Discov Today 15:958–965. https://doi.org/10.1016/j.drudis.2010.08.007

Kong B, Yu J, Savino K et al (2012) Synthesis of α-calcium sulfate hemihydrate submicron-rods in water/n-hexanol/CTAB reverse microemulsion. Colloids Surf A Physicochem Eng Asp 409:88–93. https://doi.org/10.1016/j.colsurfa.2012.05.041

Kreilgaard M (2002) Influence of microemulsions on cutaneous drug delivery. Adv Drug Deliv Rev 54:S77–S98. https://doi.org/10.1016/S0169-409X(02)00116-3
Kuentz M (2011) Oral self-emulsifying drug delivery systems, from biopharmaceutical to technical formulation aspects. J Drug Deliv Sci Technol 21:17–26. https://doi.org/10.1016/S1773-2247(11)50002-4
Lawrence MJ, Rees GD (2012) Microemulsion-based media as novel drug delivery systems. Adv Drug Deliv Rev 64:175–193. https://doi.org/10.1016/j.addr.2012.09.018
Le Marchand L (2002) Cancer preventive effects of flavonoids - a review. Biomed Pharmacother 56:296–301. https://doi.org/10.1016/S0753-3322(02)00186-5
Lehmann L, Keipert S, Gloor M (2001) Effects of microemulsions on the stratum corneum and hydrocortisone penetration. Eur J Pharm Biopharm 52:129–136. https://doi.org/10.1016/S0939-6411(01)00160-6
Liu CH, Lee WS, Wu WC (2016) Photodynamic inactivation against Pseudomonas aeruginosa by curcumin microemulsions. RSC Adv 6:63013–63022. https://doi.org/10.1039/c6ra10193c
Lopes L (2014) Overcoming the cutaneous barrier with microemulsions. Pharmaceutics 6:52–77. https://doi.org/10.3390/pharmaceutics6010052
Lopes LB, Vandewall H, Li HT et al (2010) Topical delivery of lycopene using microemulsions: enhanced skin penetration and tissue antioxidant activity. J Pharm Sci 99:1346–1357. https://doi.org/10.1002/jps.21929
Lu CT, Zhao YZ, Wong HL et al (2014) Current approaches to enhance CNS delivery of drugs across the brain barriers. Int J Nanomedicine 9:2241–2257. https://doi.org/10.2147/IJN.S61288
Lv X, Liu T, Ma H et al (2017) Preparation of essential oil-based microemulsions for improving the solubility, pH stability, photostability, and skin permeation of quercetin. AAPS PharmSciTech 18:3097–3104. https://doi.org/10.1208/s12249-017-0798-x
Magno LM, Angelescu DG, Sigle W, Stubenrauch C (2011) Microemulsions as reaction media for the synthesis of Pt nanoparticles. Phys Chem Chem Phys 13:3048–3058. https://doi.org/10.1039/c0cp01085e
Malik MA, Wani MY, Hashim MA (2012) Microemulsion method: a novel route to synthesize organic and inorganic nanomaterials. 1st Nano update. Arab J Chem 5:397–417. https://doi.org/10.1016/j.arabjc.2010.09.027
Mandal SD, Mandal S, Patel J (2016) Brain targeting efficiency of Curcumin loaded mucoadhesive microemulsion through intranasal route. J Pharm Investig 46:179–188. https://doi.org/10.1007/s40005-016-0227-2
McAllister K, Sazani P, Adam M et al (2002) Polymeric nanogels produced via inverse microemulsion polymerization as potential gene and antisense delivery agents. J Am Chem Soc 124:15198–15207. https://doi.org/10.1021/ja027759q
McClements DJ (2012) Nanoemulsions versus microemulsions: terminology, differences, and similarities. Soft Matter 8:1719–1729. https://doi.org/10.1039/c2sm06903b
Mehnert W (2001) Solid lipid nanoparticles production, characterization and applications. Adv Drug Deliv Rev 47:165–196. https://doi.org/10.1016/S0169-409X(01)00105-3
Mobasheri A, Henrotin Y, Biesalski H-K, Shakibaei M (2012) Scientific evidence and rationale for the development of curcumin and resveratrol as nutraceutricals for joint health. Int J Mol Sci 13:4202–4232. https://doi.org/10.3390/ijms13044202
Mouri A, Diat O, El Ghzaoui A et al (2014) Phase behavior of reverse microemulsions based on Peceol®. J Colloid Interface Sci 416:139–146. https://doi.org/10.1016/j.jcis.2013.10.058
Müller RH, Mäder K, Gohla S (2000) Solid lipid nanoparticles (SLN) for controlled drug delivery – a review of the state of the art. Eur J Pharm Biopharm 50:161–177. https://doi.org/10.1016/S0939-6411(00)00087-4
Nagula RL, Wairkar S (2019) Recent advances in topical delivery of flavonoids: a review. J Control Release 296:190–201. https://doi.org/10.1016/j.jconrel.2019.01.029
Nastiti CMRR, Ponto T, Abd E et al (2017) Topical nano and microemulsions for skin delivery. Pharmaceutics 9:37. https://doi.org/10.3390/pharmaceutics9040037

Nazar MF, Shah SS, Khosa MA (2011) Microemulsions in enhanced oil recovery: a review. Pet Sci Technol 29:1353–1365. https://doi.org/10.1080/10916460903502514

Padmanaban G, Rangarajan PN (2016) Curcumin as an adjunct drug for infectious diseases. Trends Pharmacol Sci 37:1–3. https://doi.org/10.1016/j.tips.2015.09.007

Pangeni R, Sahni JK, Ali J et al (2014) Resveratrol: review on therapeutic potential and recent advances in drug delivery. Expert Opin Drug Deliv 11:1285–1298. https://doi.org/10.1517/17425247.2014.919253

Parvathy KS, Negi PS, Srinivas P (2009) Antioxidant, antimutagenic and antibacterial activities of curcumin-β-diglucoside. Food Chem 115:265–271. https://doi.org/10.1016/j.foodchem.2008.12.036

Pavel FM (2004) Microemulsion polymerization. J Dispers Sci Technol 25:1–16. https://doi.org/10.1081/DIS-120027662

Peinado C, Bosch P, Martín V, Corrales T (2006) Photoinitiated polymerization in bicontinuous microemulsions: fluorescence monitoring. J Polym Sci Part A Polym Chem 44:5291–5303. https://doi.org/10.1002/pola.21649

Pepe D, Phelps J, Lewis K et al (2012) Decylglucoside-based microemulsions for cutaneous localization of lycopene and ascorbic acid. Int J Pharm 434:420–428. https://doi.org/10.1016/j.ijpharm.2012.06.016

Perlman ME, Murdande SB, Gumkowski MJ et al (2008) Development of a self-emulsifying formulation that reduces the food effect for torcetrapib. Int J Pharm 351:15–22. https://doi.org/10.1016/j.ijpharm.2007.09.015

Pillai AB, Nair JV, Gupta NK, Gupta S (2015) Microemulsion-loaded hydrogel formulation of butenafine hydrochloride for improved topical delivery. Arch Dermatol Res 307:625–633. https://doi.org/10.1007/s00403-015-1573-z

Pouton CW (2000) Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and "self-microemulsifying" drug delivery systems. Eur J Pharm Sci 11:S93–S98. https://doi.org/10.1016/S0928-0987(00)00167-6

Praça FG, Viegas JSR, Peh HY et al (2020) Microemulsion co-delivering vitamin a and vitamin E as a new platform for topical treatment of acute skin inflammation. Mater Sci Eng C 110:110639. https://doi.org/10.1016/j.msec.2020.110639

Rao J, McClements DJ (2011) Food-grade microemulsions, nanoemulsions and emulsions: fabrication from sucrose monopalmitate & lemon oil. Food Hydrocoll 25:1413–1423. https://doi.org/10.1016/j.foodhyd.2011.02.004

Rao AV, Rao LG (2007) Carotenoids and human health. Pharmacol Res 55(3):207–216. https://doi.org/10.1016/j.phrs.2007.01.012

Riccioni G (2009) Carotenoids and cardiovascular disease. Curr Atheroscler Rep 11:434–439. https://doi.org/10.1007/s11883-009-0065-z

Rigotti A (2007) Absorption, transport, and tissue delivery of vitamin E. Mol Asp Med 28:423–436. https://doi.org/10.1016/j.mam.2007.01.002

Roohinejad S, Middendorf D, Burritt DJ et al (2014a) Capacity of natural β-carotene loaded microemulsion to protect Caco-2 cells from oxidative damage caused by exposure to H2O2. Food Res Int 66:469–477. https://doi.org/10.1016/j.foodres.2014.10.012

Roohinejad S, Oey I, Everett DW, Niven BE (2014b) Evaluating the effectiveness of β-carotene extraction from pulsed electric field-treated carrot pomace using oil-in-water microemulsion. Food Bioprocess Technol 7:3336–3348. https://doi.org/10.1007/s11947-014-1334-6

Roussaki M, Gaitanarou A, Diamanti PC et al (2014) Encapsulation of the natural antioxidant aureusidin in biodegradable PLA nanoparticles. Polym Degrad Stab 108:182–187. https://doi.org/10.1016/j.polymdegradstab.2014.08.004

Sanchez-Dominguez M, Pemartin K, Boutonnet M (2012) Preparation of inorganic nanoparticles in oil-in-water microemulsions: a soft and versatile approach. Curr Opin Colloid Interface Sci 17:297–305. https://doi.org/10.1016/j.cocis.2012.06.007

Santanna VC, Curbelo FDS, Castro Dantas TN et al (2009) Microemulsion flooding for enhanced oil recovery. J Pet Sci Eng 66:117–120. https://doi.org/10.1016/j.petrol.2009.01.009

Santos P, Watkinson AC, Hadgraft J, Lane ME (2008) Application of microemulsions in dermal and transdermal drug delivery. Skin Pharmacol Physiol 21:246–259. https://doi.org/10.1159/000140228

Scalbert A, Morand C, Manach C, Rémésy C (2002) Absorption and metabolism of polyphenols in the gut and impact on health. Biomed Pharmacother 56:276–282. https://doi.org/10.1016/S0753-3322(02)00205-6

Seljak KB, Berginc K, Trontelj J et al (2014) A self-microemulsifying drug delivery system to overcome intestinal resveratrol toxicity and presystemic metabolism. J Pharm Sci 103:3491–3500. https://doi.org/10.1002/jps.24114

Shah RM, Malherbe F, Eldridge D et al (2014) Physicochemical characterization of solid lipid nanoparticles (SLNs) prepared by a novel microemulsion technique. J Colloid Interface Sci 428:286–294. https://doi.org/10.1016/j.jcis.2014.04.057

Shah B, Khunt D, Misra M, Padh H (2016) Non-invasive intranasal delivery of quetiapine fumarate loaded microemulsion for brain targeting: formulation, physicochemical and pharmacokinetic consideration. Eur J Pharm Sci 91:196–207. https://doi.org/10.1016/j.ejps.2016.05.008

Sintov AC, Shapiro L (2004) New microemulsion vehicle facilitates percutaneous penetration in vitro and cutaneous drug bioavailability in vivo. J Control Release 95:173–183. https://doi.org/10.1016/j.jconrel.2003.11.004

Smoliga JM, Baur JA, Hausenblas HA (2011) Resveratrol and health – a comprehensive review of human clinical trials. Mol Nutr Food Res 55:1129–1141. https://doi.org/10.1002/mnfr.201100143

Solans C, Kunieda H (1997) Industrial applications of microemulsions. Marcel Dekker, New York

Spernath A, Yaghmur A, Aserin A et al (2002) Food-grade microemulsions based on nonionic emulsifiers: media to enhance lycopene solubilization. J Agric Food Chem 50:6917–6922. https://doi.org/10.1021/jf025762n

Talegaonkar S, Azeem A, Ahmad F et al (2008) Microemulsions: a novel approach to enhanced drug delivery. Recent Pat Drug Deliv Formul 2:238–257. https://doi.org/10.2174/187221108786241679

Tang H, Xiang S, Li X et al (2019) Preparation and in vitro performance evaluation of resveratrol for oral self-microemulsion. PLoS One 14:e0214544. https://doi.org/10.1371/journal.pone.0214544

Terao J (2009) Dietary flavonoids as antioxidants. In: Food factors for health promotion. KARGER, Basel, pp 87–94

Thilakarathna S, Rupasinghe H (2013) Flavonoid bioavailability and attempts for bioavailability enhancement. Nutrients 5:3367–3387. https://doi.org/10.3390/nu5093367

Tønnesen HH, Másson M, Loftsson T (2002) Studies of curcumin and curcuminoids. XXVII. Cyclodextrin complexation: solubility, chemical and photochemical stability. Int J Pharm 244:127–135. https://doi.org/10.1016/S0378-5173(02)00323-X

Traber MG, Atkinson J (2007) Vitamin E, antioxidant and nothing more. Free Radic Biol Med 43:4–15. https://doi.org/10.1016/j.freeradbiomed.2007.03.024

Tsai YH, Lee KF, Huang YB et al (2010) In vitro permeation and in vivo whitening effect of topical hesperetin microemulsion delivery system. Int J Pharm 388:257–262. https://doi.org/10.1016/j.ijpharm.2009.12.051

Vicentini FTMC, Vaz MMOLL, Fonseca YM et al (2011) Characterization and stability study of a water-in-oil microemulsion incorporating quercetin. Drug Dev Ind Pharm 37:47–55. https://doi.org/10.3109/03639045.2010.491078

Walle T, Hsieh F, DeLegge MH et al (2004) High absorption but very low bioavailability of oral resveratrol in humans. Drug Metab Dispos 32:1377–1382. https://doi.org/10.1124/dmd.104.000885

Wang C, Bu Y, Zhao L (2017) Synthesis of water and oil dual-absorption materials by bicontinuous microemulsion polymerization. Polym Sci – Ser B 59:292–299. https://doi.org/10.1134/S1560090417030162

Wilhelm EA, Vogt AG, Reis AS et al (2018) The efficacy of microemulsion-based delivery to improve vitamin E properties: evaluation of the antinociceptive, antioxidant, antidepressant- and anxiolytic-like activities in mice. J Pharm Pharmacol 70:1723–1732. https://doi.org/10.1111/jphp.13018

Winsor P (1954) Solvent properties of amphiphilic compounds. Butterworths, London

Wolf S, Feldmann C (2016) Microemulsions: options to expand the synthesis of inorganic nanoparticles. Angew Chemie – Int Ed 55:15728–15752. https://doi.org/10.1002/anie.201604263

Woodside JV, McGrath AJ, Lyner N, McKinley MC (2015) Carotenoids and health in older people. Maturitas 80:63–68. https://doi.org/10.1016/j.maturitas.2014.10.012

Xiao Y, Chen X, Yang L et al (2013) Preparation and oral bioavailability study of curcuminoid-loaded microemulsion. J Agric Food Chem 61:3654–3660. https://doi.org/10.1021/jf400002x

Xing Q, Song J, You X et al (2016) Microemulsions containing long-chain oil ethyl oleate improve the oral bioavailability of piroxicam by increasing drug solubility and lymphatic transportation simultaneously. Int J Pharm 511:709–718. https://doi.org/10.1016/j.ijpharm.2016.07.061

Yen FL, Wu TH, Tzeng CW et al (2010) Curcumin nanoparticles improve the physicochemical properties of curcumin and effectively enhance its antioxidant and antihepatoma activities. J Agric Food Chem 58:7376–7382. https://doi.org/10.1021/jf100135h

Yutani R, Komori Y, Takeuchi A et al (2016) Prominent efficiency in skin delivery of resveratrol by novel sucrose oleate microemulsion. J Pharm Pharmacol 68:46–55. https://doi.org/10.1111/jphp.12497

Zhao X, Wang Z (2019) A pH-sensitive microemulsion-filled gellan gum hydrogel encapsulated apigenin: characterization and in vitro release kinetics. Colloids Surf B Biointerfaces 178:245–252. https://doi.org/10.1016/j.colsurfb.2019.03.015

Zhao X, Wang Z, Li X (2016) Preparation, in-vitro release and antioxidant potential of formulation of apigenin with hydroxypropyl-β-cyclodextrin modified microemulsion. J Incl Phenom Macrocycl Chem 86:93–102. https://doi.org/10.1007/s10847-016-0644-x