# Nanoemulsions: A Potential Advanced Nanocarrier Platform for Herbal Drug Delivery

19

Sumit Sharma, Sonali Batra, and V. R. Sinha

**Abstract**

Nanotechnology is an emerging science in pharmaceutical technology with numerous opportunities to address the various challenges in drug delivery. Despite the scientifically proved therapeutic activities and good safety and efficacy, the use of herbals is limited. This is due to challenges like higher molecular size, low aqueous solubility, lipid permeability, and elevated degradation profile in vitro and in vivo which lead to ineffective pharmacodynamic and pharmacokinetic profile. Amid the advancement in novel drug delivery systems for herbal bioactives, nanoemulsion technology is highly popular in the pharma industry. Nanoemulsion technology is the nanocarrier system which has the ability to overcome all aforesaid challenges and potentiate the biological efficacy of herbal bioactives. This chapter highlights the concept and state of the art for the nanoemulsion and describes the applications of nanoemulsions for herbal drug delivery.

**Keywords**

Nanotechnology · Herbals · Nanoemulsion · Microemulsion · Drug delivery application

S. Sharma
Delhi Pharmaceutical Sciences and Research University, New Delhi, India

S. Batra
Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar, Haryana, India

V. R. Sinha (✉)
University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India
e-mail: vrsinha@pu.ac.in; vr_sinha@yahoo.com



R. C. Sobti, N. S. Dhalla (eds.), *Biomedical Translational Research*,
https://doi.org/10.1007/978-981-16-9232-1_19

## 19.1 Introduction

Nanoemulsions are classified as nanoscale emulsions which are specifically regarded as kinetically stable systems. The nanoemulsions are optically isotropic mixtures and can be translucent or transparent. However, microemulsions are also nanoscale emulsion but are both thermodynamically and kinetically stable as compared to nanoemulsions with a droplet size of less than 100 nm. These emulsions are liquid-liquid colloidal dispersion with amphiphilic surface-active agents (Barkat et al. 2020; McClements 2012). Due to its nano-size, these novel drug delivery systems offer enhanced solubility and permeability of poorly aqueous soluble compounds (Ghai and Sinha 2012), optical clarity (de Oca-Ávalos et al. 2017), better bioavailability (Li et al. 2017), and increased shelf life (de Oca-Ávalos et al. 2017; Sharma and Sinha 2018; Parveen et al. 2015). Nanoemulsion mainly comprises three components, i.e., oleaginous phase, surface-active agents, and aqueous phase. The oleaginous phase involves the lipophilic components such as free fatty acids, mono-, di-, or triacylglycerols, essential oils, etc. The role of surface-active agents is to stabilize the nanoemulsion by preventing Ostwald ripening, coalescence, and flocculation. These surface-active molecules also prevent collision of small droplets and provide kinetic stability to nanoemulsions. Surface-active agents form a layer around the dispersed phase or droplet which can be monolayer or multilayer and reduce the interfacial tension between two immiscible liquids. Selection of surface-active agents with an appropriate hydrophilic-lipophilic balance (HLB) value is necessary as this is an important parameter which determines the type of emulsion (oil in water or water in oil). Moreover, the surface-active agents are important components of nanoemulsion which determine as well as maintain the droplet size throughout the shelf life. These surface-active molecules may be used as stabilizers, emulsifiers, wetting agents, and viscosifiers. Finally, the third component is aqueous phase which influences polarity, ionic strength, and phase behavior of nanoemulsion. Sometimes apart from the aforesaid components, cosolvents are also utilized in nanoemulsion formulation so as to increase the emulsification attribute and provide stability to the nanoemulsion. Short-chain alcohols, proteins, and carbohydrates are some of the examples that are utilized as cosolvents in nanoemulsion (Saxena et al. 2017). Amid the advancement in novel drug delivery systems for herbal bioactives, nanoemulsion technology is highly popular throughout the globe. Herbal-derived molecules or extracts have several therapeutic benefits and are scientifically proven also. But challenges like higher molecular size, low aqueous solubility, lipid permeability, and elevated degradation profile in vitro and in vivo lead to ineffective pharmacodynamic and pharmacokinetic profile. Nanoemulsion technology is the nanocarrier system which has the ability to overcome all aforesaid challenges and potentiate the biological efficacy of herbal bioactives. Also, scientific studies have meticulously provided the evidences which demonstrate dose minimization (Kazemi et al. 2020), facilitate targeting (Shobo et al. 2018; Ahmad et al. 2018), improving bioavailability (Zhao et al. 2013), release behavior (Macedo et al. 2014), and reducing side effects (Maghbool et al. 2020). In this chapter, we highlight the

concept and state of the art for the nanoemulsion and describes the applications of nanoemulsions for herbal drug delivery.

## 19.2 Nanoemulsion: The State of the Art

Among the formulation considerations, nanoemulsions formulated with low-energy methods relatively require high concentration of surface-active agents as compared to the high-energy methods. A drawback of destabilization of micelles is associated with higher concentration of surfactants utilized for the fabrication of nanoemulsions by low-energy method. Such methods utilize only environmental changes and form a spontaneous nanoemulsification system. On the other hand, high-energy methods utilize intensive mechanical forces such as high-pressure homogenization/microfluidization and ultrasonic waves. These intensive disruptive forces break down the large droplets of dispersed phase into smaller droplets. Therefore, the high-energy methods require relatively less concentration of surfactants as intensive mechanical forces facilitate the size reduction of micelles (Salvia-Trujillo et al. 2016). Also, microemulsions due to its thermodynamic stability generally require low-energy methods for preparation (Nastiti et al. 2017). The surface-active agents can be ionic (anionic or cationic or zwitterionic) or nonionic (neutral) in nature and depending on the nature these agents impart stability to nanoemulsions. For instance, ionic emulsifiers induce electrostatic repulsion and prevent dispersed phase aggregation. On the other hand, nonionic emulsifiers predominantly induce steric hindrance and reduce droplet aggregation (Aswathanarayan and Vittal 2019). Nanoemulsions are nonequilibrium type of system which cannot be formed spontaneously, and external energy input is required to process the formulation. This external energy facilitates to circumvent the challenge of interfacial tension between the immiscible liquids and form kinetically stable nanoscale emulsified droplets for a long time (Aboofazeli 2010). The importance of additional shear is to break the micron size droplets into nano-range. The high shear required for formulating nanoemulsions is due to the inverse relation of Laplace pressure with the curvature radius (nonplanar surface), and mathematically it is denoted as $\Pi_L = 2\sigma/r$ (Bhattacharjee 2019; Mason et al. 2006). The $\Pi_L$ refers as Laplace pressure, $\sigma$ as interfacial tension between two immiscible liquids, and $r$ as droplet radius. Laplace pressure is defined as the pressure exerted by curved interface on the molecules inside the droplet. This also signifies that smaller droplets have relatively high Laplace pressure than larger droplets. Furthermore, nanoemulsions are thermodynamically unstable and have positive value of Gibbs free energy on the formation of nano-droplets. This is due to significant increase in surface area of while conversion from large size droplets (micron/submicron) to small droplets. Consequently, the magnitude for the change in the surface area of dispersed phase becomes positive, and entropy of formed nanoemulsion is also more than zero or positive. Hence, referring the following mathematical equation (Eq. 19.1), Gibbs free energy for formed nanoemulsion becomes positive which signifies that the formation of nanoemulsion is a non-spontaneous process (Barkat et al. 2020):

$$\Delta G = \Delta Ar\gamma + T\Delta S \tag{19.1}$$

where
$\Delta G$ is the Gibbs free energy or total free energy
$\gamma$ is the interfacial tension
$\Delta Ar$ is the change in the surface area of the interface
$T$ is the temperature of the system
$\Delta S$ is the change in entropy

## 19.3 Types of Nanoemulsion

Nanoemulsions are mainly classified as oil in water (o/w), water in oil (w/o), and bicontinuous phases. In principle, among the two immiscible liquids, one component will be dispersed phase and the other will be regarded as continuous phase. By convention, the phase with higher volume fraction becomes the continuous phase and the other will become dispersed phase, but it is dependent on the type of the emulsifier. Accordingly, the surfactant molecules will orient themselves around the dispersed phase and impart kinetic stability. The nonpolar tail part of the surfactant orients towards the hydrophobic phase, whereas the polar head towards the hydrophilic phase. Hydrophilic-lipophilic balance (HLB) is a parameter which aids in the selection of appropriate surfactant. HLB of a surfactant signifies a ratio of hydrophilic segment to the lipophilic segment. This means the lower the HLB value (around 3–8), the surfactant is more suited for the preparation of w/o type nanoemulsion, and higher HLB (around 8–18) forms o/w nanoemulsion (Che Marzuki et al. 2019). In the case of bicontinuous phase, both immiscible liquids do not form globules in the dispersion; instead, they form irregular structures or birefringence. This state is also known as liquid crystalline state.

## 19.4 Components of Nanoemulsion

### 19.4.1 Oil

Oil is one of the components of nanoemulsion and is employed to solubilize hydrophobic drug molecules. Also, oil phase facilitates drug permeation through the biological membrane of the gastrointestinal tract or skin and improves pharmacokinetic behavior. In association with surfactants, oil phase tends to emulsify and form nano-micelles with hydrophobic drug in solubilized form. In general, for pharmaceutical use, hydrolyzed vegetable oils, chemically modified triglycerides, essential oils, and medium-chain fatty acids are preferred. The screening of oil is done on the basis of drug solubility in oil phase, and also miscibility with surfactant is also evaluated before the final selection of all excipients.

### 19.4.2 Surfactants and Cosurfactants

The surfactants or cosurfactants are also known as surface-active agents, and they can be nonionic, cationic, anionic, and zwitterionic. The role of surfactant is to determine the type of emulsion, size of dispersed droplet, and stability and sometimes also impart toxicity to the nanoemulsion. Among the toxicity issues, the excess amount of surfactants may cause gastric irritancy if taken orally, skin hypersensitivity in topical use, and renal toxicity in parenteral use. Therefore, it is necessary to critically monitor the type and concentration of surfactants while preparing nanoemulsions for pharmaceutical use. Surfactant alone is not sufficient to reduce interfacial tension and stabilize nanoemulsion. Therefore, an additional cosurfactant is usually required for the preparation of nanoemulsion. Preferably, C3–C8 chain alcohols (ethanol, glycerin, propylene glycol, polyethylene glycol 400, Transcutol P) are employed as cosurfactant and are supposed to increase the fluidity as well as synergistically reduce the interfacial tension (Lawrence 1996). Generally, cosurfactants are needed in lower concentrations as compared to the surfactant. For instance, in the preparation of o/w nanoemulsion with one surfactant, a small area signifying the nanoemulsion region has been observed. However, in combination with suitable cosurfactant, an increase in the nanoemulsion region towards the water-rich apex has been observed. Also, more oil can be transformed into nanoemulsified droplets. Therefore, a proper optimization of surfactant mixture has to be validated so that surfactant and cosurfactant mixture can provide an optimum reduction in interfacial tension (Sharma 2018) (Table 19.1).

## 19.5 Technology Involved for Preparing Nanoemulsion

Nanoemulsions are a non-spontaneous and non-equilibrated system, which means they require some extra energy to form. Nanoemulsion comprises numerous nanodroplets which cause an increase in the surface area, and to increase the surface area, additional energy input is required. Therefore, to fabricate nanoemulsion, the type of constituents, processing methods (high-energy or low-energy method), and processing conditions are the critical factors among the nanoemulsion formulation considerations. The primary aim is to achieve the minimum interfacial tension with maximum stabilizing capacity and small size. In some cases, the mixture formed spontaneously by mixing components all together is coarse dispersion, and hence such premixtures are then subjected to high-energy processes like high-pressure homogenization, microfluidization, and ultrasonication. These methods have different mechanisms to reduce the size from coarse to significantly small size range as shown in Fig. 19.1. High-energy methods utilize mechanical devices to forcefully break down the bigger droplets to ultrasmall size. On the other hand, low-energy processes comparatively require low energy input, and size reduction is carried out by phase inversion composition, phase inversion temperature, and solvent diffusion method. Low-energy processes generally utilize the intrinsic properties of the components.

**Table 19.1** Some examples of components of microemulsion/nanoemulsion used for herbal drug delivery

| Oils | Surfactant/ cosurfactant | Concentration | Application | References |
|---|---|---|---|---|
| Cassia oil | Tween 20, ethanol | Cassia oil/ethanol/ Tween 20 (1: 3:6) | Antifungal activity | Xu et al. (2012) |
| Clove oil | Tween 20 | Clove oil/Tween 20/water (5: 30:65) | Antiparasitic activity | Gupta et al. (2005) |
| Neem oil | Tween 80, sodium dodecyl benzene sulfonate, and hexyl alcohol | Neem oil/emulsifiers/ water (1:3.5: 5.5) | Antiparasitic activity | Xu et al. (2010) |
| *Origanum vulgare* essential oil | Tween 60, butylene glycol | Oil/Tween 60/butylene glycol/water (5:25:25:45) | Anti-inflammatory property | Laothaweerungsawat et al. (2020) |
| Artemisinin loaded in a eutectic oil mixture of lidocaine and ibuprofen | Tween 80, Span 20, and ethanol in a ratio of 1:1:1 | 1% of artemisinin loaded in oil phase; oil/surfactant/ water (1:4.5: 4.5) | Transdermal delivery system | Zhang et al. (2020) |
| Curcumin in vitamin E oil | Tween 20 and ethanol | Vitamin E/Tween 20/ethanol/ water (3.3: 53.8:6.6:36.3) | Improved solubility, stability, and oral availability | Bergonzi et al. (2014) |
| Piperine solubilized in Capryol 90 | Cremophor RH 40, Tween 80, and Transcutol HP | o/w emulsion: Capryol 90/$S_{mix}$/water (32:34:34) w/o emulsion: Capryol 90/$S_{mix}$/water (64:27:9) | Oral delivery of piperine for the treatment of Alzheimer's disease | Etman et al. (2018) |
| Berberine in oleic acid | Tween 80, PEG 400 | Oleic acid/ Tween 80/PEG 400/water (15: 17:17:51) | Oral drug delivery system | Gui et al. (2008) |
| Capsaicin solubilized in medium-chain triglycerides (MCT) | Cremophor EL, ethanol | MCT/ Cremophor EL/ethanol/ water (1.0:7.2: 1.8:20.5) | Enhanced oral bioavailability | Zhu et al. (2015) |

(continued)

**Table 19.1** (continued)

| Oils | Surfactant/ cosurfactant | Concentration | Application | References |
|---|---|---|---|---|
| Tea tree oil | Polysorbate 80, isopropyl myristate, isopropyl alcohol | Tea tree oil (5%) | Anti-psoriatic activity | Khokhra Sonia (2011) |

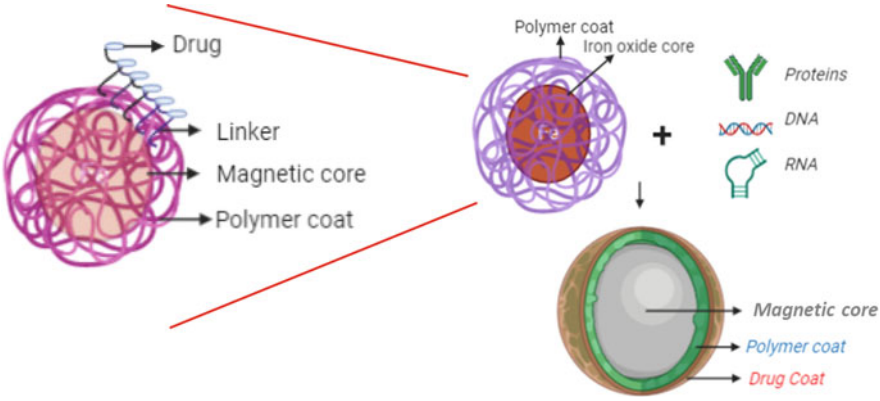


**Fig. 19.1** Overview of method of preparation for nanoemulsions

### 19.5.1 High-Energy Processes

These methods mainly involve mechanical energy in the form of pressure, wave, or mechanical stirring. After disruption of coarse dispersion into very small droplets and increasing the surface area, the process allows adsorption of surfactants at the interface of and enables steric stabilization. The magnitude of mechanical energy must be significantly greater than the interfacial energy so as to achieve a nano-range of droplets. The following are the generally employed high-energy processes for the fabrication of nanoemulsions.

#### 19.5.1.1 High-Pressure Homogenization

The principle of nanoemulsification through high-pressure homogenization involves passing the fluid through micro-orifice under positive pressure through the homogenizer valve. In this process, shear, impact, and cavitation are the principal mechanisms producing mechanical energy to disrupt the droplets into smaller size (Shen 2012; Villalobos-Castillejos et al. 2018). The method involves mainly a two-step process where in the first step, coarse droplets are reduced to ultrafine droplets with an increased surface area. After size reduction to nano-range, the droplets tend to undergo coalescence. Hence, the second step involves the role of the emulsifier wherein the emulsifier adsorbs on the interface and reduces the interfacial tension. An increase in emulsifier concentration and faster adsorption retard the coalescence

process and impart stability to nanoemulsion. The process of homogenization is performed in cycles and optimized. During homogenization, sometimes heat is generated which may have a detrimental effect on heat-sensitive bioactives. However, this situation can be countered through ice or cold water jacketing and reducing the homogenization time of each cycle.

#### 19.5.1.2 Microfluidization

The microfluidization process utilizes a static and mechanical mixer which involves driving a fluid through microchannels under high pressure which results in ultrafine droplets of dispersed phase. The positive pressure applied has a direct impact on size reduction, which means an increase in pressure may result in a decrease in droplet size. The principle of microfluidization is almost similar to high-pressure homogenization except the passage through microchannels whose pore size ranges from 50 to 300 μm. Generally, a pressure of around 270 mPa is applied in microfluidization, and the fluid is allowed to move downstream through microchannels at a velocity of approximately 400 m/s. Through the inlet, the fluid passes through the Y junction where it splits into two branches and then reconnects at the interaction chamber at high velocity and high shear rate. After size reduction, the surface area of dispersed phase increased significantly, and the surfactant has to adsorb on the interface rapidly to avoid coalescence. Therefore, fast-adsorbing surfactants are often selected for fabricating nanoemulsions through microfluidization. Also, increasing the viscosity of continuous phase also retards the coalescence of ultrafine droplets. These forces result in mechanical energy with high magnitude sufficient to counter the interfacial energy and significantly reduce the droplet size (Che Marzuki et al. 2019; Villalobos-Castillejos et al. 2018).

#### 19.5.1.3 Ultrasonication

Among other high-energy methods, ultrasonication is the simplest, is easy to use, and requires low-end mechanical instruments. It is the ultrasound waves that are responsible to produce shock waves, resulting in disruption of mainly oil droplets into smaller size in water. These intensive ultrasonic waves generate vibrations and acoustic cavitation which creates high pressure in dispersed phase and turbulence that collapse the droplets. The frequency of sonic waves and time of sonication play an important role for appropriate size reduction. An optimum frequency is necessary to produce shock waves with sufficient high energy input that can disrupt the droplet. Generally, frequency with more than 20 KHz is suitable for droplet size reduction. Also, the more the time of ultrasonication, the more efficiently size reduction takes place. This is because an increase in the time of ultrasonication produces higher energy input capable to reduce the interfacial tension (Behrend et al. 2000).

### 19.5.2 Low-Energy Processes

Low-energy processes are of great interest for those bioactives which are heat sensitive as in the case of high-energy processes, some of the heat energy is

produced. On the other hand, low-energy processes, particularly the phase inversion composition and solvent diffusion method, show spontaneous emulsification with slight agitation. All methods of low-energy processes depend on inherent physicochemical properties of all components to form nanoemulsions such as solubility, concentration, and impact of temperature. Unlike the high-pressure energy process, the low-energy process does not utilize high energy input for reducing interfacial tension which may generate additional heat in the system. This approach for the fabrication of nanoemulsion recommends the use of medium-chain triglycerides for oily phase, whereas these methods are not suitable for long-chain triglycerides. Hence, this limits the use of several oils in which the herbal bioactive shows good solubility. But this situation can be resolved in some of the cases by using a mixture of medium-chain and long-chain triglycerides (Pathania et al. 2018).

#### 19.5.2.1 Phase Inversion Temperature

In this method, a key role is played by the emulsifier which tends to change their hydrophilic and lipophilic character with respect to temperature at fixed concentration. With an increase in temperature, the emulsifier changes their curvature at the interface, and the process of phase inversion begins. For instance, o/w nanoemulsion is subjected to higher temperature, and with an increase in temperature, the solubility of the emulsifier tends to alter. Particularly, the solubility of nonionic surfactant decreases in aqueous solution with an increase in temperature due to the dehydration of the hydrophilic component of nonionic surfactant. Therefore, at a specific temperature, the type of nanoemulsion reversed, i.e., from o/w to w/o nanoemulsion, due to the change in the solubility of the emulsifier as a function of time. This temperature is known as phase inversion temperature. A continuous stirring is generally required in this technique for the uniform distribution of temperature in the system and ultimately the uniform influence of temperature on size reduction. Comparatively, higher concentration of the emulsifier (such as ceteareth-12, cetostearyl alcohol, and tetra-ethylene glycol dodecyl ether) is required in this method as it is mainly the inherent property of the emulsifier which is influenced by temperature that plays a critical role in phase inversion, droplet size, type of emulsion, and stability (Pathak 2017; Anton and Vandamme 2009; Förster et al. 1990).

#### 19.5.2.2 Phase Inversion Composition

This is a type of low-energy method wherein the change in fraction of oil to water or vice versa at fixed temperature leads to phase inversion. The mechanism involved a change in emulsifier orientation with an increase in dispersed phase volume. Due to the change in emulsifier orientation, the micelle transformed from one type to another, i.e., o/w to w/o or vice versa. The process involves slow addition of one component with slight stirring. In between the complete transition, a phase comes where the content of both oil and water reaches almost in equal fractions. Bicontinuous structures are formed in this phase and are also known as liquid crystalline phase. After this phase further addition of oil or water forms the opposite type of micelle and with an increase in dilution results a further droplet size reduction (Sharma and Sinha 2018; Che Marzuki et al. 2019; Sharma 2018).

#### 19.5.2.3 Solvent Diffusion Method

In solvent diffusion method, oily components are mixed into organic solvents like ethanol, acetone, ethyl acetate, isopropyl acetate, etc. The prepared oily phase is then mixed in aqueous phase consisting of surfactant or surfactant mixture with continuous stirring. The agitation caused by the stirring in the system forms nano-droplets. The organic solvent is then removed from the system using rotary vacuum evaporator. The safety consideration of organic solvent is important in this method as the solvent has to be safe in terms of toxicity. Also, the solvent should have miscibility with both the oil and aqueous phases. The concentration of organic solvent along with the concentration of oil, surfactant, and water plays an influential role in the determining the formation of nanoemulsion and its stability (Porras et al. 2008; Bouchemal et al. 2004).

## 19.6 Application of Nanoemulsion for Herbal Bioactives

Herbal bioactives have been pharmacologically utilized for the treatment of various diseases. Despite the huge potential of phytopharmaceuticals (herbal extracts and bioactives), their pharmaceutical application is limited due to poor water solubility, membrane permeability, and limited bioavailability. All these issues can be resolved through nanoemulsion technology wherein the active compound is encapsulated in nano-droplets dispersed in continuous medium. Also, self-nanoemulsifying system has the property to transform into nano-droplets when comes in contact with gastric environment and additional energy required for the formation of nanoemulsion is provided by the gastrointestinal motility itself. Such type of nanoemulsions is also known as self-emulsifying nanoemulsion. The dispersed phase rapidly diffuses into the continuous phase and instantaneously forms nanoscale emulsions in vivo. Such nanoscale emulsions usually carry low oil content and high concentration of surfactant or surfactant mixture which enables to form o/w nanoemulsion spontaneously (Kumar et al. 2019). Nanoemulsion also provides stability to phytopharmaceuticals from gastric degradation and can also impart controlled release pharmacokinetics. Several herbal phytopharmaceuticals (quercetin, camptothecin, rutin, genistein, resveratrol) have been reported to be delivered using nanoemulsion technology primarily with an aim to improve their permeability through the gastrointestinal membrane and skin (Salvia-Trujillo et al. 2016; McClements and Xiao 2017; Aboalnaja et al. 2016; Rahman et al. 2020).

The important challenge associated with phytopharmaceuticals is their variable bioavailability that may produce nonuniform therapeutic effects. This is the reason phytopharmaceuticals are unable to produce favorable therapeutic action consistently and sometimes cannot satisfy the medical community. This nonuniformity causes uncertainty in treating disease and reduced level of significance in statistical clinical data. There are mainly three major factors that influence the oral bioavailability of phytopharmaceuticals, i.e., (1) the dose of the herbal extract or bioactive to be ingested and fraction available for dissolution in gastric environment (this factor can be a rate-limiting factor for most of the herbal bioactives because of their

hydrophobicity that limits their solubilization in vivo); (2) fraction of the solubilized concentration which is supposed to be absorbed through the gastrointestinal membrane and enter into the systemic circulation (in this factor, the permeability factor plays a key role that determines the level of absorption); and (3) after absorption through oral route, the absorbed fraction undergoes biotransformation and then transferred to the site of action.

Therefore, several novel drug delivery approaches have been concurrently performed and developed to maximize the therapeutic efficacy of herbal bioactives. Apart from solubility, permeability, and stability issues of phytopharmaceuticals, improvising the biological half-life is of great concern among the formulation scientists. As biological half-life directly determines the bioavailability and potency of herbal bioactives at the site of action. Low biological half-life signifies low bioavailability and high biological half-life signifies high bioavailability (Mukherjee et al. 2015).

To curb all aforesaid problems associated with herbal bioactives, nano-sized emulsions are pioneering among the novel drug delivery systems (NDDS) in context to industrial viability and providing promising uniform therapeutic results to clinicians. The herbal bioactives are usually lipophilic or have poor aqueous solubility which generally limits their bioavailability. Hence, nanoemulsions are the best suitable drug carrier system as the hydrophobic bioactive substance is dissolved in oil phase, whereas the hydrophilic bioactive is dissolved in aqueous phase. After solubilizing the bioactive in selective phase (oil/water) along with appropriate surfactant and cosurfactant are mixed into the continuous phase. The colloidal dispersion formed is subjected to either high-energy processes or low-energy processes for nanoemulsification or size reduction. In some cases co-solvents are also added as an adjuvant as they have been shown to increase the solubility of compounds and penetration into biological tissues as well. In such cases, transforming the bioactive substance into a crystalline form can resolve the issue (Chen et al. 2011; Shegokar and Müller 2010). It has been observed that most of the herbal bioactives are usually poorly soluble in oil and water as discussed in Table 19.2. Under such circumstances, the route of administration plays a key role in defining the formulation considerations. For instance, if the hydrophobic bioactive is intended to deliver through oral route, then the oily phase is preferred as it tends to digest rapidly in the gastrointestinal medium and forms mixed micelles also known as swollen micelles (Rana et al. 2017). In the case of topical or transdermal route, certain percutaneous absorption enhancers like ethanol or essential oils are reported as an adjuvant to nanoemulsion (Shen et al. 2011). Also, for topical applications, the increased concentration of surfactants or cationic surfactants can be employed for improvising the low solubility and permeability issues with clinical safety (Dario et al. 2016).

Selection of oil also plays a major role particularly for drug loading and ultimately bioavailability of lipophilic herbal actives. The oils with long-chain triglycerides comprise comparatively more lipophilic character due to long nonpolar chains. This property allows accommodation of more drug into the mixed micelle formed and nanoemulsification technology facilitates the dissolution and permeability through

**Table 19.2** Some of the examples of herbal bioactives formulated as nanoemulsion

| Herbal extract/ bioactive | Therapeutic activity | Route of administration | Pharmaceutical challenge | NDDS technology | Method of preparation | Outcomes | References |
|---|---|---|---|---|---|---|---|
| Mangiferin (xanthone glycoside) | Anti-inflammatory | Topical | Low aqueous solubility (experimentally approximately 2 mg/mL at 30°C) | Hyaluronic acid (low molecular weight) assisted o/w nanoemulsion gel with globule size ~290 nm | High-energy emulsification method using homogenization followed by ultrasonication | Presence of low molecular weight HA in combination with Transcutol P has significantly increased in vitro permeation of mangiferin | Pleguezuelos-Villa et al. (2019), Acosta et al. (2016) |
| Silymarin (flavonoid) | Hepatoprotective drug, free radical scavenger, and oxidase enzyme inhibitor | Oral | Low oral bioavailability (<47%) | o/w nanoemulsion using Capryol 90 (oil), Solutol HS 15 (surfactant), and Transcutol HP (cosurfactant) with globule size ~50 nm | High-pressure homogenization followed by ultrasonication | Enhanced bioavailability of silymarin was observed with nanoemulsion as compared to oral suspension | Nagi et al. (2017), de Groot and Rauen (1998) |
| Quercetin (flavonoid) | Antioxidant | Topical as hair conditioner | Low water solubility (~50 μM) | Cationic o/w nanoemulsion with average globule size ~20 nm | Low-energy process using phase inversion temperature | High drug loading up to 0.5% w/w and stable at room temperature and ~5°C | Dario et al. (2016) |
| Myricetin (flavonoid) | Antioxidant | Oral | Low oral bioavailability (<10%) and aqueous solubility (~16.60 g/mL) | Self-nanoemulsifying drug delivery system using Capryol 90 (oil), Cremophor RH 40 (surfactant), and polyethylene glycol | Low-energy process | Improved solubility and permeability in duodenum and jejunum as compared to free drug | Qian et al. (2017) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | 400, 1,2-propanediol, and Transcutol HP (cosurfactant) with globule size ranging between 20 and 140 nm | | | |
| Zedoary turmeric oil (essential oil comprising mainly sesquiterpenes) | Antibacterial, antithrombotic, hepatoprotective, and increase gastrointestinal motility | Oral | Poor water solubility, irritant, and unstable in the gastrointestinal environment; also high volatility as a consequence reduced drug loading in solid dosage forms | Self-nanoemulsifying drug delivery system using ethyl oleate (oil), Tween 80 (surfactant), Transcutol P (cosurfactant) with ~30% drug loading and a globule size of ~68 nm | Low-energy process | Oral bioavailability of bioactive marker (germacrone) of zedoary turmeric oil increased significantly in rats as compared to unformulated zedoary turmeric oil | Song and Sun (2016), Zhao et al. (2010) |
| Colchicine (alkaloid) | Potent anti-inflammatory | Oral | Low aqueous solubility and membrane permeability | Eugenol (absorption enhancer) assisted o/w nanoemulsion using isopropyl myristate and eugenol (oil), Tween 80 (surfactant), and ethanol with average globule size ~40 nm | Low-energy process | Increased bioavailability due to eugenol-based nanoemulsion as compared to free drug solution | Shen et al. (2011) |
| Ferulic acid (4-hydroxy-3-methoxycinnamic acid) | Potent antioxidant, anti-inflammatory, antiaging, free | Topical | Limited solubility in water and oils | o/w nanoemulgel with isostearyl isostearate (oil), Labrasol (surfactant), and | Spontaneous emulsification followed by ultrasonication | Improved solubility, permeability, and UV protection | Harwansh et al. (2015), Batra et al. |

(continued)

**Table 19.2** (continued)

| Herbal extract/ bioactive | Therapeutic activity | Route of administration | Pharmaceutical challenge | NDDS technology | Method of preparation | Outcomes | References |
|---|---|---|---|---|---|---|---|
| | radical scavenging activity, antiatherogenic, antianxiety, neuroprotective, and cardioprotective | | | Plurol isostearique (cosurfactant) with globule size ranging between 100 and 200 nm, resulting in sustained release, better permeability, and antioxidant activity | | activity and showed sustained release profile | (2018), Sonali et al. (2020) |
| β-Carotene (carotenoid) | Singlet oxygen scavenger, precursor of vitamin A | Oral | Low aqueous solubility, low bioavailability, high melting point, and highly susceptible to autoxidation due to the presence of conjugated polyunsaturated hydrocarbon chain | o/w nanoemulsion using corn oil, β-lactoglobulin (surfactant), and EDTA | High-pressure microfluidization | Increased stability against the color fading of carotenoids and reduced rate of degradation | Qian et al. (2012b), Padmanabhan et al. (2016) |
| Lycopene (carotenoid) | Potent antioxidant, singlet oxygen, and free radical quencher | Oral | Sensitive to chemical degradation and undergo oxidation on storage | o/w nanoemulsions using sesame oil, linseed oil, or walnut oil as the oil phase and lactoferrin (emulsifier) with globule size ~200 nm | High-pressure homogenization | Reduced oxidative degradation during digestive process, thereby resulting in increased bioaccessibility and improved efficacy | Zhao et al. (2020) |

the biological membrane (Qian et al. 2012a; Yang and McClements 2013). Such micelles with comparatively large dimension of nonpolar chains also facilitate loading of large hydrophobic bioactives and capable to transport these large hydrphobic molecules across the biological membrane. Some of the oils like tocopherols have antioxidant property which can be utilized for imparting the stability to bioactives which are sensitive to oxidation such as carotenoids. Ethylenediaminetetraacetic acid and ascorbic acid are some other water-soluble examples of antioxidants which are commonly utilized in nanoemulsions for providing chemical stability to sensitive bioactives (Qian et al. 2012b). Herbal bioactives like resveratrol with short half-life in water and susceptible to aqueous degradation can be formulated as nanoemulsion (Francioso et al. 2014). Nanoemulsions by encapsulating the bioactive in oil phase not only increase the shelf life but also slow down the degradation kinetics of resveratrol when administered orally and hence improve the bioavailability (Davidov-Pardo and McClements 2015). In conclusion, nanoemulsions as a drug delivery system for herbal bioactives are the ideal approach for hydrophobic herbal bioactives as it addresses major challenges of poor water solubility, low permeability, chemical degradation, and reduced bioaccessibility. Moreover, nanoemulsions are suitable for oral, topical, and pulmonary route of administration and hence prove its wide acceptance. Oil solubility, water solubility, miscibility of oil and surfactants, polarity, viscosity, optical clarity, stability, crystal form of bioactive, and partition coefficient are some of the important formulation considerations that should be taken into account while formulating nanoemulsions for bioactives.

## 19.7 Future Prospects

The amalgamation of nanotechnology with herbal bioactives is quintessential in the current scenario. Nanoemulsions, among all the nanocarrier systems, use industrially viable and comparatively low-end mechanical instruments for its fabrication; hence, it is widely accepted and used. The benefits of herbal bioactives are effectively delivered with the help of nanoemulsions, especially dealing with low-solubility criteria which most of the natural products have. Nanoemulsions offer great advantages as they can formulate herbal bioactives and the route of administration can vary from oral, topical, as well as parenteral. Improved targeting, reduced size, increased solubility, as well as better bioavailability are some of the major criteria for a formulation to be efficient. Nanoemulsions inculcate all these features and effectively deliver herbal bioactives without altering their health benefits. With the upcoming renewal of the use of herbal moieties, it becomes the need of the situation to effectively deliver the bioactives. This is thus possible with the exploration of the systematic and effective approach for the formulation of such bioactives. Nanoemulsions have been widely used in many such cases and have shown tremendous results in nanoresearch. Thus, this collaboration of nanoemulsions with herbal bioactives holds immense potential for future, providing formulation experts a pathway to enhance in the field of nanoresearch.

## References

Aboalnaja KO et al (2016) Utilization of nanoemulsions to enhance bioactivity of pharmaceuticals, supplements, and nutraceuticals: nanoemulsion delivery systems and nanoemulsion excipient systems. Expert Opin Drug Deliv 13(9):1327–1336

Aboofazeli R (2010) Nanometric-scaled emulsions (nanoemulsions). Iran J Pharm Res 9(4): 325–326

Acosta J et al (2016) Determination of mangiferin solubility in solvents used in the biopharmaceutical industry. J Pharm Pharmacogn Res 4:49–53

Ahmad N et al (2018) Intranasal delivery of quercetin-loaded mucoadhesive nanoemulsion for treatment of cerebral ischaemia. Artif Cells Nanomed Biotechnol 46(4):717–729

Anton N, Vandamme TF (2009) The universality of low-energy nano-emulsification. Int J Pharm 377(1):142–147

Aswathanarayan JB, Vittal RR (2019) Nanoemulsions and their potential applications in food industry. Front Sustain Food Syst 3:95

Barkat MA et al (2020) Therapeutic nanoemulsion: concept to delivery. Curr Pharm Des 26(11): 1145–1166

Batra S, Kumar A, Sharma A (2018) Isolation, characterization and antianxiety activity of pentacosan-13-ol from Ferula sumbul Hook. Roots. J Biol Act Prod Nat 8(3):171–179

Behrend O, Ax K, Schubert H (2000) Influence of continuous phase viscosity on emulsification by ultrasound. Ultrason Sonochem 7(2):77–85

Bergonzi M et al (2014) Optimization, characterization and in vitro evaluation of curcumin microemulsions. LWT Food Sci Technol 59:148–155

Bhattacharjee K (2019) Importance of surface energy in nanoemulsion. In: Koh KS, Wong VL (eds) Nanoemulsions – properties, fabrications and applications [Internet]. IntechOpen, London. [cited 2022 Mar 02]. Available from: https://www.intechopen.com/chapters/66762. https://doi.org/10.5772/intechopen.84201

Bouchemal K et al (2004) Nano-emulsion formulation using spontaneous emulsification: solvent, oil and surfactant optimisation. Int J Pharm 280(1):241–251

Che Marzuki NH, Wahab RA, Abdul Hamid M (2019) An overview of nanoemulsion: concepts of development and cosmeceutical applications. Biotechnol Biotechnol Equip 33(1):779–797

Chen H et al (2011) Nanonization strategies for poorly water-soluble drugs. Drug Discov Today 16(7–8):354–360

Dario MF et al (2016) A high loaded cationic nanoemulsion for quercetin delivery obtained by sub-PIT method. Colloids Surf A Physicochem Eng Asp 489:256–264

Davidov-Pardo G, McClements DJ (2015) Nutraceutical delivery systems: resveratrol encapsulation in grape seed oil nanoemulsions formed by spontaneous emulsification. Food Chem 167: 205–212

de Groot H, Rauen U (1998) Tissue injury by reactive oxygen species and the protective effects of flavonoids. Fundam Clin Pharmacol 12(3):249–255

de Oca-Ávalos JMM, Candal RJ, Herrera ML (2017) Nanoemulsions: stability and physical properties. Curr Opin Food Sci 16:1–6

Etman SM et al (2018) Oral brain-targeted microemulsion for enhanced piperine delivery in Alzheimer's disease therapy: in vitro appraisal, in vivo activity, and nanotoxicity. AAPS PharmSciTech 19(8):3698–3711

Förster T, Schambil F, Tesmann H (1990) Emulsification by the phase inversion temperature method: the role of self-bodying agents and the influence of oil polarity. Int J Cosmet Sci 12(5):217–227

Francioso A et al (2014) Improved stability of trans-resveratrol in aqueous solutions by carboxymethylated (1,3/1,6)-β-D-glucan. J Agric Food Chem 62(7):1520–1525

Ghai D, Sinha VR (2012) Nanoemulsions as self-emulsified drug delivery carriers for enhanced permeability of the poorly water-soluble selective β1-adrenoreceptor blocker Talinolol. Nanomedicine 8(5):618–626

Gui SY et al (2008) Preparation and evaluation of a microemulsion for oral delivery of berberine. Pharmazie 63(7):516–519
Gupta S et al (2005) Designing and testing of an effective oil-in-water microemulsion drug delivery system for in vivo application. Drug Deliv 12(5):267–273
Harwansh RK et al (2015) Enhanced permeability of ferulic acid loaded nanoemulsion based gel through skin against UVA mediated oxidative stress. Life Sci 141:202–211
Kazemi M et al (2020) Deep skin wound healing potential of lavender essential oil and licorice extract in a nanoemulsion form: biochemical, histopathological and gene expression evidences. J Tissue Viability 29(2):116–124
Khokhra Sonia DA (2011) Microemulsion based transdermal drug delivery of tea tree oil. Int J Drug Devel Res 3(1):191–198
Kumar M et al (2019) Techniques for formulation of nanoemulsion drug delivery system: a review. Prev Nutr Food Sci 24(3):225–234
Laothaweerungsawat N et al (2020) Transdermal delivery enhancement of carvacrol from Origanum vulgare L. essential oil by microemulsion. Int J Pharm 579:119052
Lawrence MJ (1996) Microemulsions as drug delivery vehicles. Curr Opin Colloid Interface Sci 1(6):826–832
Li Y-J et al (2017) Nanoemulsion-based delivery system for enhanced oral bioavailability and Caco-2 cell monolayers permeability of berberine hydrochloride. Drug Deliv 24(1):1868–1873
Macedo AS et al (2014) Nanoemulsions for delivery of flavonoids: formulation and in vitro release of rutin as model drug. Pharm Dev Technol 19(6):677–680
Maghbool M et al (2020) The effects of eugenol nanoemulsion on pain caused by arteriovenous fistula cannulation in hemodialysis patients: a randomized double-blinded controlled cross-over trial. Complement Ther Med 52:102440
Mason TG et al (2006) Nanoemulsions: formation, structure, and physical properties. J Phys Condens Matter 18(41):R635–R666
McClements DJ (2012) Nanoemulsions versus microemulsions: terminology, differences, and similarities. Soft Matter 8(6):1719–1729
McClements DJ, Xiao H (2017) Designing food structure and composition to enhance nutraceutical bioactivity to support cancer inhibition. Semin Cancer Biol 46:215–226
Mukherjee PK, Harwansh RK, Bhattacharyya S (2015) Chapter 10 – Bioavailability of herbal products: approach toward improved pharmacokinetics. In: Mukherjee PK (ed) Evidence-based validation of herbal medicine. Elsevier, Boston, pp 217–245
Nagi A et al (2017) Quality by design based silymarin nanoemulsion for enhancement of oral bioavailability. J Drug Deliv Sci Technol 40:35–44
Nastiti R et al (2017) Topical nano and microemulsions for skin delivery. Pharmaceutics 9:37
Padmanabhan P, Cheema A, Paliyath G (2016) Solanaceous fruits including tomato, eggplant, and peppers. In: Caballero B, Finglas PM, Toldrá F (eds) Encyclopedia of food and health. Academic Press, Oxford, pp 24–32
Parveen R et al (2015) Stability studies of silymarin nanoemulsion containing Tween 80 as a surfactant. J Pharm Bioallied Sci **7**(4):321–324
Pathak M (2017) Chapter 5 – Nanoemulsions and their stability for enhancing functional properties of food ingredients. In: Oprea AE, Grumezescu AM (eds) Nanotechnology applications in food. Academic Press, pp 87–106
Pathania R et al (2018) Essential oil nanoemulsions and their antimicrobial and food applications. Curr Res Nutr Food Sci J 6:626–643
Pleguezuelos-Villa M et al (2019) Mangiferin nanoemulsions in treatment of inflammatory disorders and skin regeneration. Int J Pharm 564:299–307
Porras M et al (2008) Properties of water-in-oil (W/O) nano-emulsions prepared by a low-energy emulsification method. Colloids Surf A Physicochem Eng Asp 324(1):181–188
Qian C et al (2012a) Nanoemulsion delivery systems: influence of carrier oil on β-carotene bioaccessibility. Food Chem 135(3):1440–1447

Qian C et al (2012b) Inhibition of β-carotene degradation in oil-in-water nanoemulsions: influence of oil-soluble and water-soluble antioxidants. Food Chem 135(3):1036–1043
Qian J et al (2017) Self-nanoemulsifying drug delivery systems of myricetin: formulation development, characterization, and in vitro and in vivo evaluation. Colloids Surf B: Biointerfaces 160: 101–109
Rahman HS et al (2020) Novel drug delivery systems for loading of natural plant extracts and their biomedical applications. Int J Nanomedicine 15:2439–2483
Rana S et al (2017) Chapter 7 – Interfacial engineering of nanoparticles for cancer therapeutics. In: Ficai A, Grumezescu AM (eds) Nanostructures for cancer therapy. Elsevier, pp 177–209
Salvia-Trujillo L, Martín-Belloso O, McClements DJ (2016) Excipient nanoemulsions for improving oral bioavailability of bioactives. Nanomaterials (Basel, Switzerland) 6(1):17
Saxena A et al (2017) Chapter 7 – Technological aspects of nanoemulsions and their applications in the food sector. In: Oprea AE, Grumezescu AM (eds) Nanotechnology applications in food. Academic Press, pp 129–152
Sharma S (2018) Formulation and development of site specific delivery systems of cyclosporine and curcumin for inflammatory bowel disorders. University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India
Sharma S, Sinha VR (2018) Liquid nanosize emulsion-filled enteric-coated capsules for colon delivery of immunosuppressant peptide. AAPS PharmSciTech 19(2):881–885
Shegokar R, Müller RH (2010) Nanocrystals: industrially feasible multifunctional formulation technology for poorly soluble actives. Int J Pharm 399(1–2):129–139
Shen L (2012) Microfluidization as a potential technique to modify surface properties of soy protein isolate. Food Res Int 48:108–118
Shen Q, Wang Y, Zhang Y (2011) Improvement of colchicine oral bioavailability by incorporating eugenol in the nanoemulsion as an oil excipient and enhancer. Int J Nanomedicine 6:1237–1243
Shobo A et al (2018) Enhanced brain penetration of pretomanid by intranasal administration of an oil-in-water nanoemulsion. Nanomedicine (Lond) 13(9):997–1008
Sonali B, Ashwani K, Anupam S (2020) GABA and 5-HT receptor mediated anxiolytic effect of essential oil of Ferula sumbul Hook. Roots. Nat Prod J 10(3):262–271
Song T, Sun R (2016) Pharmacodynamics study of zedoary turmeric oil chitosan microspheres administered via arterial embolization. Artif Cells Nanomed Biotechnol 44(8):1958–1963
Villalobos-Castillejos F et al (2018) Chapter 8 – Fabrication of nanoemulsions by microfluidization. In: Jafari SM, McClements DJ (eds) Nanoemulsions. Academic Press, pp 207–232
Xu J et al (2010) The preparation of neem oil microemulsion (Azadirachta indica) and the comparison of acaricidal time between neem oil microemulsion and other formulations in vitro. Vet Parasitol 169:399–403
Xu SX et al (2012) In vitro and in vivo antifungal activity of a water-dilutable cassia oil microemulsion against Geotrichum citri-aurantii. J Sci Food Agric 92(13):2668–2671
Yang Y, McClements DJ (2013) Vitamin E bioaccessibility: influence of carrier oil type on digestion and release of emulsified α-tocopherol acetate. Food Chem 141(1):473–481
Zhang Y et al (2020) Enhancement of transdermal delivery of artemisinin using microemulsion vehicle based on ionic liquid and lidocaine ibuprofen. Colloids Surf B Biointerfaces 189:110886
Zhao Y et al (2010) Self-nanoemulsifying drug delivery system (SNEDDS) for oral delivery of Zedoary essential oil: formulation and bioavailability studies. Int J Pharm 383(1–2):170–177
Zhao L et al (2013) Nanoemulsion improves the oral bioavailability of baicalin in rats: in vitro and in vivo evaluation. Int J Nanomedicine 8:3769–3779
Zhao C et al (2020) Encapsulation of lycopene within oil-in-water nanoemulsions using lactoferrin: impact of carrier oils on physicochemical stability and bioaccessibility. Int J Biol Macromol 153:912–920
Zhu Y et al (2015) In vitro and in vivo evaluation of capsaicin-loaded microemulsion for enhanced oral bioavailability. J Sci Food Agric 95(13):2678–2685