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Recent advances in encapsulation of curcumin in nanoemulsions: A review of
encapsulation technologies, bioaccessibility and applications

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Abstract

Curcumin is widely acknowledged for its beneficial activities. However, its application has remained challenging due to its low aqueous solubility, biochemical/ structural degradation and poor bioavailability. For these reasons, many researches are aimed at overcoming these limitations using lipid-based nanosystems to encapsulate curcumin, especially nanoemulsions. This review highlights the theoretical aspects and recent advances of preparation technologies (phase inversion temperature, phase inversion composition, ultrasonication, high pressure homogenization and microfluidization) for encapsulation of curcumin in nanoemulsions. Additionally, the specific factors in designing nanoemulsions systems that affect the chemical stability and *in vitro* bioaccessibility of the encapsulated curcumin are discussed. Also, the importance of nanoemulsions in improving antioxidant, anti-inflammatory and anticancer activities of curcumin is underlined. Curcumin-loaded nanoemulsions preparation technologies have been proposed to provide efficient, systematic, and practical protocols for improved applications of curcumin. Additionally, key factors that influence curcumin delivery include the nature of emulsifier, the type and the amount of carrier oil and emulsifier-curcumin interactions. The pharmacological activities of curcumin including antioxidant, anti-inflammatory and anticancer activities can be improved by nanoemulsions resulting in better functional efficacy.

Keywords: Curcumin; Encapsulation; Nanoemulsions; Bioaccessibility; Applications

Abbreviations: TPA, 12-O-tetradecanoylphorbol-13-acetate; AP-1, activator protein-1; CYP3A2, cytochrome P450 3A2; DME, direct membrane emulsification; DTAB, dodecyltrimethylammonium bromide; GIT, gastrointestinal tract; GMO, glycerol monooleate; GMS, glycerol monostearate; HPH, high pressure homogenization; HLB,

hydrophilic-lipophilic balance; IL-1 β , interleukin-1 β ; LCT, long chain triacylglycerols; MCT, medium chain triglycerides; NF- κ B, nuclear factor κ B; O/W, oil-in-water; Pgp, p-glycoprotein; PIC, phase inversion composition; PIT, phase inversion temperature; PEG 400, polyethylene glycol; PME, premix membrane emulsification; ROS, reactive oxygen species; SCT, short chain triacylglycerols; SGF, simulated gastric fluid; SIF, simulated intestinal fluids; SSF, simulated saliva fluid; TABRS, thiobarbituric acid reactive substances; TNF- α , tumor necrosis factor- α ; W/O, water-in-oil; W/O/W, water-in-oil-in-water

1. Introduction

Curcumin is a natural low-molecular-weight (368.37g mol⁻¹) polyphenolic compound present in the *Curcuma longa* (turmeric) rhizomes (Rafiee, Nejatian, Daeihamed, & Jafari, 2019). Turmeric is a wide-spread spice, typical of Indian cooking, that also found use in traditional Indian and Chinese medicines. Curcuminoids are the essential components of turmeric, which are responsible for its yellow color. Turmeric rhizomes contain 3~5% four types of curcuminoid derivatives including curcumin (77%), demethoxycurcumin (17%), bisdemethoxycurcumin (3%) and cyclocurcumin, of which curcumin is the most important bio-active constituent (Araiza-Calahorra, Akhtar, & Sarkar, 2018; Wakte et al., 2011).

Over the last few decades, curcumin has received considerable interest owing to its wide range of pharmaceutical functions and biological features. Curcumin can be used as a flavouring substance (bitter taste), as a food preservative, as a natural colorant (bright yellow color) and as an antioxidant in various foods and beverages (Eybl, Kotyzova, & Koutensky, 2006; Wakte et al., 2011). Numerous studies have explored the applications of curcumin in prophylaxis and treatment of a variety of inflammatory conditions including wound healing in cutaneous (Mohanty, Das, & Sahoo, 2012; Nguyen et al., 2019; Phan, See, Lee, & Chan, 2001), excisional (Jagetia & Rajanikant, 2012; Mun et al., 2013) and chronic wounds (Kant et al., 2015) and pro-inflammatory chronic diseases such as neurodegenerative diseases (Ghosh,

Banerjee, & Sil, 2015; Lv et al., 2014; Mourtas, Lazar, Markoutsas, Duyckaerts, & Antimisiaris, 2014), cardiovascular diseases (Hasan et al., 2014; Sahebkar, 2015), autoimmune diseases (Arora, Kuhad, Kaur, & Chopra, 2015; Rivera-Mancía, Lozada-García, & Pedraza-Chaverri, 2015), gastrointestinal disorders (Morsy & El-Moselhy, 2013; Sah, Jha, Sah, Shah, & Yadav, 2013) and psychological diseases (Jiang et al., 2013). Anti-cancer activities of curcumin has also been extensively investigated and supporting evidences were found for its potential use in chemoprevention and treatment of a wide variety of tumors including breast (Liu & Ho, 2018), gastrointestinal (Jakubek et al., 2019; Rajasekaran, 2011), melanoma (Wang et al., 2017) and sarcoma (M. Singh, Pandey, Karikari, Singh, & Rakheja, 2010). In spite of its excellent pharmacological benefits, researchers are still facing difficulties related to its poor water solubility, chemical instability, photodegradation, relatively high rate of metabolic degradation, rapid metabolism and rapid elimination from the body, and low oral bioavailability (Hussain, Thu, Amjad, et al., 2017; Anand, Kunnumakkara, Newman, & Aggarwal, 2007). Additionally, curcumin shows poor adsorption owing to its lipophilic nature. To overcome these problems, new strategies have been employed for improving its functional properties. Incorporation of curcumin into nanocarriers by different techniques is a suitable and efficient option (Araiza-Calahorra et al., 2018; Hussain, Thu, Ng, Khan, & Katas, 2017). Particularly, nanoemulsions have been described as excellent carriers of lipophilic curcumin, to improve its stability and bioavailability.

In order to produce homogenous nanoemulsions, different processes (e.g., phase inversion temperature, phase inversion composition, ultrasonication, high pressure homogenization and microfluidization, etc.) have been developed. The preparation methods play an important role in loading and encapsulation efficiency of curcumin, as well as droplet size after curcumin incorporation. In this sense, suitable methodologies are needed to obtain nanoemulsions of

different sizes, structures and properties to achieve different applications. Also, a scale-up to a higher level of production is necessary for industrial applications.

Hence, there is an essential need to extensively discuss the recent advances in different methods for the preparation of curcumin-loaded nanoemulsions. Additionally, we present in this review the specific factors in designing nanoemulsions system that affect the chemical stability and *in vitro* bioaccessibility of the encapsulated curcumin. Finally, antioxidant, anti-inflammatory and anticancer activities of such curcumin-loaded nanoformulations are comprehensively underlined.

2. Properties of curcumin and their limitations in applications

2.1. Structural characteristics and chemistry properties of curcumin

Curcumin, also known as diferuloyl methane, is a symmetric molecule, with an ordered crystal structure (Araiza-Calahorra et al., 2018; Sun et al., 2018). The structure of curcumin is comprised of two aromatic rings with methoxyl and hydroxyl groups in the ortho position, connected through a seven carbon chain consisting of an α , β -unsaturated β -diketone moiety (Sahne, Mohammadi, Najafpour, & Moghadamnia, 2017). The molecular configuration of curcumin can exist in the tautomeric forms keto and enol due to intramolecular hydrogen atoms transfer at the β -diketone chain of curcumin. The structural features of curcumin are illustrated in Fig. 1. Under slightly acidic and neutral conditions, the keto form is dominant. However, in alkaline conditions, curcumin is present primarily in its enolic form (Ghosh et al., 2015; Prasad, Gupta, Tyagi, & Aggarwal, 2014). In fact, the conformation of curcumin is dependent of temperature, polarity and the properties of solvent (de Souza Ferreira & Bruschi, 2019).

Curcumin is a relatively hydrophobic molecule with a calculated log octanol/water partition coefficient (logP) value of 3.2, which makes it practically insoluble in water and highly soluble in lipid (Jamwal, 2018). It has adequate transmembrane permeability due to its

lipophilic nature (Hussain, Thu, Amjad, et al., 2017). However, curcumin is soluble in polar solvents like methanol, acetone, ethanol and dimethyl sulfoxide (DMSO) (Araiza-Calahorra et al., 2018). Besides, it is sensitive to environmental conditions, including elevated temperatures, light, extreme pH, moisture, and oxygen. Under these conditions, the three active sites (one diketone moiety, and two phenolic groups) of curcumin can suffer oxidation, especially the phenol-OH functional group which is the most easily abstractable hydrogen from curcumin. Then, the hydrogen donation reactions result in reversible and irreversible nucleophilic addition (Michael reaction) reactions, hydrolysis, degradation and enzymatic reactions (Priyadarsini, 2014). In general, the chemical degradation of curcumin in solution leads to the formation a series of compounds, such as trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal, vanillin, ferulic acid and feruloylmethane (Typek et al., 2019).

2.2. Challenges for curcumin delivery

A major problem associated with the applications of curcumin is its poor bioavailability as a result of the chemical stability, low water solubility as well as poor absorption and rapid metabolism. The bioavailability of curcumin is determined by its bioaccessibility. Curcumin needs to be bioaccessible to be absorbed by the gastrointestinal tract (GIT) epithelium cells and then transported into the systemic circulation to exert biological activities. For that, absorption of the curcumin in the GIT is crucial. However, most of curcumin through orally consumed can not be absorbed into the small intestine epithelium cells due to the hydrophobic property of curcumin. Even though part of curcumin can absorb into the epithelium cell, it can be flushed back into the lumen through the efflux system (Sanidad, Sukamtoh, Xiao, McClements, & Zhang, 2019). Moreover, after oral administration, most of curcumin is degraded in tissues such as those of the liver and small intestine before entering the systemic circulation because of the rapid metabolism (H. R. Park, Rho, & Kim, 2019).

Numerous studies have shown the low oral bioavailability of curcumin through evaluated the level of curcumin or its metabolites in serum or tissue after administration. In animal studies, Pan et al. (Pan, Huang, & Lin, 1999) reported that after intraperitoneal administration of curcumin at a dose of 0.1 g/kg body weight to mice, the levels of curcumin in the plasma, liver, intestines, kidneys, spleen and brain were 2.25, 26.90, 177.04, 7.51, 26.06 and 0.41 μ g/g, respectively. Marczylo et al. (Marczylo et al., 2007) also showed poor bioavailability of curcumin. They found that the maximum serum concentration of curcumin, curcumin sulfate and curcumin glucuronide were 6.5 ± 4.5 nM, 225 ± 0.6 nM and 7.0 ± 11.5 nM, respectively after oral dosing of 340 mg/kg curcumin to rats. In a clinical trial of curcumin treatment for patients with colorectal cancer, neither curcumin nor its metabolites were detected in blood or urine with an oral dose of 440~2200 mg/day curcumin extract at up to 29 days of daily treatment, but curcumin and curcumin sulfate were found in feces (Sharma et al., n.d.). Similarity, human studies also show that curcumin has poor bioavailability. In a human Phase II clinical trial, only 22~41 ng/mL curcumin was detected in the plasma of patients with pancreatic cancer who had received 8 g/day of curcumin by mouth (Dhillon et al., 2008). More recently, Hiroki et al. (Sasaki et al., 2011) found that after an oral dose of 30 mg/kg curcumin powder, maximum curcumin concentration in plasma was 1.8 ng/mL after 6 h of dosing.

The poor solubility in water, instability at physiological pH and low oral bioavailability hinder its industrial use. However, curcumin may be encapsulated by a number of efficient encapsulation techniques, which include nanoemulsions, to improve its water solubility, stability and bioavailability.

3. Methods of preparation of curcumin-loaded nanoemulsions

Nanoemulsions are biphasic dispersion of two immiscible phases with one dispersed in the other: either water in oil (W/O) or oil in water (O/W) droplets stabilized by an amphiphilic

surfactant (Y. Singh et al., 2017). Typically, nanoemulsions are defined with a very small droplet size ($r < 100$ nm) (Salvia-Trujillo, Martín-Belloso, & McClements, 2016), and because they are nonequilibrium systems, their formation requires energy. The generation of nanoemulsions can be achieved through two essentially different approaches: (i) low-energy and (ii) high-energy methods (Y. Yang, Marshall-Breton, Leser, Sher, & McClements, 2012). Low-energy emulsification makes use of internal chemical energy of the system, which allows to produce small droplets without or with a gentle stirring (Ren et al., 2019). In contrast, high-energy production methods rely on mechanical devices (e.g. microfluidizer, high-pressure homogenizer, etc.) to produce intense disruptive forces that break up particles into smaller sizes (Ren et al., 2019; Y. Yang et al., 2012). These low energy emulsification methods have gained more attention in recent years due to lower operational costs and equipment investments compared with high energy methods (Borrin, Georges, Moraes, & Pinho, 2016). Moreover, they may be less detrimental to heat sensitive bioactive compounds.

3.1. Low-energy emulsification methods

Low-energy methods include many different methods, such as phase inversion and self-emulsification. The phase inversion methods often involve the inversion of the surfactant curvature from positive to negative or negative to positive (Calderó et al., 2016; Solans & Solé, 2012). This can be achieved through two different routes: changing the temperature while keeping the constant composition (Phase Inversion Temperature, PIT), and changing the composition while keeping the constant temperature (Phase Inversion Composition, PIC) (Calderó et al., 2016; Ren et al., 2019).

3.1.1. Phase inversion temperature method

The PIT method is based on a phase transition by the change in the nonionic surfactant spontaneous curvature induced by temperature. At low temperatures, the temperature-sensitive surfactants are hydrophilic and have a positive spontaneous curvature.

In contrast, the surfactants are more hydrophobic and the spontaneous curvature tends to become negative with increasing temperatures. At intermediate temperatures (hydrophilic-lipophilic balance -temperature), the hydrophilic and lipophilic properties of surfactants are balanced, and the mean spontaneous curvature is close to zero (Ren et al., 2019; Sharif, Astaraki, Azar, Khorrami, & Moradi, 2012). The affinity of the surfactant for the aqueous and oil phases is exchanged by varying temperature, causing a change in phase from water-in-oil (W/O) to oil-in-water (O/W) (Boscán, Barandiaran, & Paulis, 2018). A schematic representation of the PIT method to form O/W nanoemulsions can be observed in [Fig. 2a](#). First an O/W emulsion is prepared by mixing of all components (surfactant, cosurfactant, oil and water, etc.) at room temperature, then gently heating the system to above or around the PIT temperature followed by rapidly cooling down to spontaneously form fine oil droplets. The PIT temperature, is defined as the temperature where the mixed system has a low turbidity due to the formation of a bicontinuous emulsion (Chuesiang et al., 2019). It is commonly determined by measuring the electrical conductivity, since there is a drastic difference between the electrical conductivity values of the oil phase and water phase (de Oliveira Honse et al., 2018). pH is another property that can be used to evaluate the PIT temperature. In general, at the temperature above the PIT, the pH of the system is unstable and can not be measured. However, the pH is always stable while below the PIT (Mashhadi, Javadian, Tyagi, Agarwal, & Gupta, 2016).

Recently, several groups have reported the formation of curcumin-loaded nanoemulsions by PIT method ([Table1](#)). Jintapattanakit et al. (Jintapattanakit, Hasan, & Junyaprasert, 2018) prepared curcuminoid-loaded nanoemulsions with a nonionic surfactant, polyethylene glycol-40 hydrogenated castor oil (RH40) through the PIT method. The effect of curcuminoid and RH40 concentrations on the particle size, zeta potential and stability was investigated in detail. The results show that the PIT method may be more efficient than other methods for the

production of edible nanoemulsions using RH40 as the surfactant. Calligaris et al. (Calligaris et al., 2017) also obtained curcumin-loaded nanoemulsions by the PIT method. They demonstrated that the maximum lipid content allowing curcumin loaded transparent microemulsions was greatly affected by the oil type and physical state of lipid. This study contributes to the design and formation of curcumin-loaded nanoemulsions, while giving an interesting approach for the delivery of lipophilic compounds.

3.1.2. Phase inversion composition method

The PIC method is based on changing the water/oil ratio of the system through progressively adding one of the components (water or oil) over a mixture of the other components at a constant temperature during the procedure to obtain nanoemulsions (Solans & Solé, 2012). The preparation of O/W nanoemulsions by the PIC method can be divided into two steps: (i) mixing of the organic phase (oil + surfactant) to obtain a fixed composition and (ii) adding water resulting in the formation of O/W nanoemulsions (Fig. 2b). The mechanism is similar to the temperature-induced curvature change in the PIT method. Water addition leads to a progressively increase in the hydration grade of the surfactant, and the spontaneous curvature of surfactant changes from negative to positive (Roger, 2016).

Maestro et al. (Maestro, Solè, González, Solans, & Gutiérrez, 2008) developed nanoemulsions of oleylamine using oleylammonium as surfactant by the PIC method. The formation of nanoemulsion was studied in an ionic system instead of previous cationic systems. The method has been intensively investigated for nanoemulsions preparation (Solè et al., 2010; H. J. Yang, Cho, & Park, 2009; Yu, Li, Xu, Hao, & Sun, 2012). Nevertheless, no report can be found in the literature related to fabrication of curcumin-loaded nanoemulsion using PIC method. The operation steps of PIC method are quite straightforward, and the technique is easy to be scaled. Therefore, it could be a promising method for producing curcumin-loaded nanoemulsions.

3.2. High-energy emulsification methods

In recent decades, high-energy methods have been the most studied processes. A variety of high-energy methods have been proposed in the literature for preparing emulsions, including high pressure homogenization (HPH), microfluidization and ultrasonication. Compare with low-energy approaches, high-energy methods are often more effective at producing small droplet sizes as nanoemulsions are generated using mechanical devices with intensive disruptive forces, and they can use various types of oils and emulsifiers. Promising formulations for curcumin nanoemulsions have been formulated with high energy methods.

3.2.1. Ultrasonication

Ultrasonication is an effective method for reducing the emulsion mean droplet diameter. In ultrasound emulsification, the energy is supplied by a sonotrode (sonicator probe) containing a piezoelectric quartz crystal (Jafari, Assadpoor, He, & Bhandari, 2008). The tip of the sonicator probe must be placed in the center of the premix emulsion, at a certain immersion depth in the sample (Fig. 3a). The ultrasound treatments are performed for different times at different frequencies and different powers, and the temperature is controlled using a cold water bath that dissipates the heat generated during the process. During ultrasonication, micro-bubbles are contracted and expanded due to ultrasonic waves throughout the liquid medium generating compressive and tensile stresses. The formation and collapse of these bubble (vapor cavities) in a flowing liquid result in cavitation, thereby rupturing the dispersed droplets (Modarres-Gheisari, Gavagsaz-Ghoachani, Malaki, Safarpour, & Zandi, 2019).

This technique has been used by several authors to generate curcumin-loaded nanoemulsions (Table1). In the study of Páez-Hernández et al. (Páez-Hernández, Mondragón-Cortez, & Espinosa-Andrews, 2019), the effects of processing parameters (power, amplitude and treatment time) and formulation parameters (diverse types of oil and oil volume fraction) were evaluated to produce curcumin-loaded nanoemulsions using hydroxylated lecithin as the

emulsifier agent. The increase of time, amplitude, power and oil volume fraction caused decrease of mean droplet size and polydispersity index. The mean droplet sizes of the curcumin-MCT emulsion were significantly lower than the curcumin-grapeseed and curcumin-olive emulsions. Nevertheless, the zeta potential of the emulsions had similar values independent of the processing parameters used. Abbas et al. (Abbas, Bashari, Akhtar, Li, & Zhang, 2014) developed food-grade curcumin-loaded nanoemulsions stabilized by modified starches by ultrasonication. In their work, impacts of major emulsification process variables and formulation parameters on the mean droplet diameter, polydispersity index and charge on the emulsion droplets were investigated. In another work, Sari et al. (Sari et al., 2015) prepared curcumin-MCT nanoemulsions via ultrasonication using whey protein concentrate 70 and Tween 80 as emulsifiers. The encapsulation efficiency of curcumin in the nanoemulsions reached $90.56 \pm 0.47\%$. The curcumin-loaded nanoemulsions showed a good stability and improved bioaccessibility. These studies indicated that the ultrasound-assisted emulsification could be successfully used for the preparation of curcumin-loaded nanoemulsions. However, drawbacks of ultrasonication are related to the low volumes that can be prepared, and the difficulty of scaling-up.

3.2.2. High pressure homogenization

HPH is a widely used technique to produce stable O/W emulsions with fine texture. In the process, a high pressure pump (regularly up to 100 MPa) is used to pass the fluid through a narrow gap of a valve (Fig. 3b). Fluids are subjected to a wide range of forces, such as intense shear, cavitation, turbulent flow and temperature, resulting in disruption of droplets (Modarres-Gheisari et al., 2019). In most emulsion productions, HPH can be divided in two steps: (i) converting oil and water phases into a coarse emulsion; and (ii) preparing the final fine emulsion through high-pressure systems (Peng et al., 2015).

Many studies have investigated nanoencapsulation of curcumin by HPH (Table1). For

example, Mistry et al. (Mistry, Mohapatra, & Dash, 2012) prepared a curcumin delivery system via HPH using two different emulsifiers (polyvinyl alcohol (PVA) and poloxamer 407). They investigated the impacts of the HPH process and emulsifiers on the physicochemical properties of glycerol monooleate (GMO)/chitosan nanoemulsions. The particle size of the nanoemulsion was reduced to 50–65% after three cycles of HPH. It was concluded that HPH effectively reduced the particle size of the GMO/chitosan nanoemulsions loaded with curcumin. Similarly, Ma et al. (Ma et al., 2017) encapsulated curcumin using HPH in three various oil phases (i.e. MCT, canola oil and linseed oil) and three different emulsifiers (i.e. Tween-80, lecithin, whey protein isolation and acacia). They revealed correlation between emulsifier type, oil phase and physicochemical properties (curcumin content, particle size, potential, physical stability and storage stability) of curcumin formulations. Curcumin-MCT nanoemulsions achieved the maximum curcumin content compare to other oils. The increase of oil phase concentration led to increase curcumin content, particle size and viscosity of the emulsions but decrease stability. However, oil type and concentration have no significant effect on zeta-potential of curcumin nanoemulsions. In a recent work by Silva et al. (Silva et al., 2019), O/W nanoemulsions for encapsulation of curcumin were obtained by HPH using whey protein isolate as surfactant with MCT as lipid phase. Multilayer nanoemulsions were then formed by the deposition of a chitosan layer onto curcumin nanoemulsions. Both nanosystems (nanoemulsions and multilayer nanoemulsions) showed a considerable stability under storage conditions and at stomach pH conditions. Moreover, the curcumin-loaded nanosystems exhibited enhanced antioxidant activity and increased bioaccessibility compared to the free curcumin. Therefore, HPH can be used to create curcumin-loaded nanoemulsions and so improve the properties of curcumin.

3.2.3. Microfluidization

Microfluidization is one of the most efficient method of producing nanoemulsions with small

droplets. Conventional microfluidizers typically use a two-steps procedure to produce nanoemulsions: (i) forming the initial coarse emulsion by blending the oil and water phases; and (ii) producing the final fine emulsion by passing coarse emulsion through the microfluidizer (Bai, Huan, Gu, & McClements, 2016; Bai & McClements, 2016). The coarse emulsion enters the homogenizer using a high pressure pumping device, then it is divided into two streams that flow through narrow channels to impinge on each other at high velocities, thereby producing extremely intense disruptive forces (turbulence, stresses, shear and cavitation) that lead to generation of fine emulsion (Bai et al., 2016) (Fig. 3c). In addition, a one-step dual channel microfluidization method was also used to fabricate nanoemulsions.

The oil and aqueous phases were separately fed into the microfluidizer from two inlet reservoirs, then they flew through the homogenizer (Bai & McClements, 2016) (Fig. 3d).

Recently, there have been many studies applying microfluidization to produce stable curcumin-loaded nanoemulsions (Table1). In a study conducted by Raviadaran et al.(Raviadaran, Chandran, Shin, & Manickam, 2018), stable palm oil-based O/W nanoemulsions loading curcumin were successfully formulated using a microfluidizer. A response surface methodology with three independent factors (pressure, number of cycles and surfactant concentration (Tween 80)) was carried out to determine the optimum conditions for the droplet size based on the single-factor experimental results. The mean droplet size decreased with increased surfactant concentration and operating pressure. More cycles were needed to achieve smaller droplet size at lower operating pressure. However, when droplet size reached its minimum values, the number of cycles had no significant effects. In this study, the microfluidizer generated nanoemulsions with droplet size ranging 200 nm–300 nm at operating pressure of 350 bar and beyond 5 cycles. Also, Pérez-Hernández et al. (Pérez-Hernández et al., 2019) formulated curcumin-loaded nanoemulsions via microfluidization using different formulations and process parameters to evaluate their effect

on droplet size, zeta-potential, and polydispersity of the emulsions. The impact of operating pressure and number of cycles on particle size was similar to the results observed by Raviadaran et al. (Raviadaran et al., 2018) as mentioned previously. Based on these results, the optimal curcumin emulsion produced by microfluidization had a nanometric size, high negative zeta potential and low polydispersity value. In another study, Artiga-Artigas et al. (Artiga-Artigas, Lanjari-Pérez, & Martín-Belloso, 2018) prepared nanoemulsions containing curcumin through microfluidization using different surfactants. The curcumin-loaded nanoemulsions produced had a suitable physicochemical characteristics regarding particle size (≤ 400 nm), zeta potential (≤ -37 mV) and encapsulation efficiency ($\geq 75\%$). Moreover, the curcumin -encapsulated emulsion showed a good antioxidant capacity. Hence, microfluidization can be suggested as a suitable technology to produce curcumin nanoemulsions.

3.2.4. Membrane emulsification

Membrane emulsification is a promising technique to produce emulsions with a small size and a narrow droplet size distribution. It is a more recent process that also uses mechanical forces but with lower energy input compared to other emulsification methods (Alliod, Messenger, Fessi, Dupin, & Charcosset, 2019; Arkoumanis, Norton, & Spyropoulos, 2019). The low energy requirement leads to low temperature increase during the process of emulsification which gives better stability to temperature sensitive substances (Alliod et al., 2018). Mainly, two types of membrane emulsification process have been developed: direct membrane emulsification (DME) and premix membrane emulsification (PME). In DME, the dispersed phase is passed through a microporous membrane into an agitating or cross-flowing continuous phase to produce small size nanodroplets. In PME, droplets are formed by introducing the prepared coarse emulsion (premix) through a porous membrane. A schematic representation of DME and PME to form O/W nanoemulsions is shown in [Fig. 3e](#) and [Fig. 3f](#).

PME has several advantages compared to DME (Alliod et al., 2018; Santos, Vladislavljević, Holdich, Dragosavac, & Muñoz, 2015): (i) the mean droplet size is smaller than in DME; (ii) the dispersed phase flux is higher than in DME; (iii) the process parameters are easier to control than in DME.

For the formation of nanoemulsions, membrane emulsifications are particularly attractive, especially PME. In PME, the droplet size is affected by membrane properties (e.g., pore size, thickness, tortuosity, porosity and hydrophilicity/hydrophobicity), process parameters (e.g., transmembrane pressure and rotational velocity), formulation characteristics (surfactant type and concentration, dispersed phase volume fraction, emulsion viscosity) (Arkoumanis et al., 2019; Nazir, Schroën, & Boom, 2013). Several studies have investigated the impact of these factors (Table 1). For instance, Alliod et al. (Alliod et al., 2019) prepared O/W and W/O nanoemulsions by extruding a coarse emulsion through Shirasu Porous Glass (SPG) membranes with a mean pore diameter of 0.5 μm , and investigated the effect of viscosities (continuous phase viscosity, dispersed phase viscosity as well as dispersed phase content) on the membrane pressure and droplet size. The dispersed phase viscosity had a lower impact on the membrane pressure, and no significant influence on the droplet size; the continuous phase viscosity and the emulsion viscosity both had a significant impact on the membrane pressure and mean droplet size (the pressure through the membrane increased with the continuous phase viscosity and dispersed phase content, and the mean droplet size decreased with increased continuous phase viscosity and dispersed phase content). In another work by Alliod et al. (Alliod et al., 2018), the effect of process parameters (cycle number, membrane pore size, flowrate) on droplet size of O/W emulsion was investigated. In this study, only one cycle was sufficient to produce droplets with small size. The mean droplet size decreased with decreasing membrane pore size. Thus, the droplet size can be controlled by changing the pore size. Regarding membrane length, the shortest membrane led to smaller droplets as it required

higher pressure than the longer membrane. The droplet size decreased with increasing flowrate. This may be due to the higher wall shear stress applied at higher flowrate. Several other studies have shown that nanoemulsions prepared by PME had good physicochemical characteristics (droplet size, narrow size distribution, encapsulation efficiency) and exhibited a considerable stability (Berendsen, Güell, & Ferrando, 2015; Gehrman & Bunjes, 2016, 2017; Joseph & Bunjes, 2012). To the best of our knowledge, there are no studies reporting the formulation of curcumin-loaded nanoemulsions by PME method.

4. Stability and bioaccessibility of curcumin-loaded nanoemulsions

4.1. Chemical stability of curcumin-loaded nanoemulsions

In nanoemulsion delivery systems, curcumin molecules are typically located within the hydrophobic interior of the oil droplets, but some of them may also be located close to the oil–water interface due to the polar groups on the curcumin. In this case, curcumin is protected from active substances within the aqueous phase that would typically promote its chemical degradation (Sanidad et al., 2019). Therefore, the chemical stability of curcumin is enhanced by encapsulating it in nanoemulsions. Some effects of nanoemulsions on stability of curcumin have been presented in [Table 2](#).

Zheng et al. (Zheng, Zhang, Chen, Luo, & McClements, 2017) assessed the impact of different delivery system (aqueous dimethyl solutions, O/W nanoemulsions, and filled hydrogel beads) on the chemical stability of curcumin under both acidic and neutral conditions. After 14 days of storage at 55 °C, the yellowness (b^* value) of the curcumin emulsion decreased to 33% of its original value at pH 3 and to 93% of its original value at pH 7, while the yellowness of the curcumin solutions decreased to 17% of its original value at pH 3 and to 73% of its original value at pH 7. In this study, the changes of yellow color intensity indicated that curcumin degradation occurred. Xu et al. (Xu, Wang, & Yao, 2017) observed that about 25% of curcumin degraded after 40 days storage at 37 °C in the dark for curcumin

nanoemulsions prepared with casein and soybean soluble polysaccharide complex. However, the curcumin degradation in curcumin solutions was about 94% after 2 days of storage at 37 °C in the dark. Curcumin storage stability in nanoemulsions was significantly better than in solutions confirming that nanoemulsions are an efficient system to protect curcumin from chemical degradation by avoiding the interaction between curcumin molecules and other reactive substances within solutions.

The composition and structure of delivery systems significantly affect curcumin stability. Various studies have revealed that the stability of curcumin is influenced by the nature and concentration of emulsifier. Kharat et al. (Kharat, Zhang, & McClements, 2018) evaluated the impact of emulsifier type (sodium caseinate, Tween 80, quillaja saponin, gum arabic) and concentration (critical and excess) on the stability of curcumin-loaded nanoemulsions. They observed that the degradation of curcumin in saponins-stabilized nanoemulsions was relatively rapid after 15 days of storage due to the fact that saponins containing conjugated double bonds generated free radicals that promote peroxidation reactions, while the other three emulsifiers behave fairly similarly. The authors also reported that the emulsifier level in the emulsions did not significantly affect the curcumin degradation since most of the excess emulsifier was remained in the aqueous phase. Similarly, Artiga-Artigas et al. (Artiga-Artigas et al., 2018) assessed the impact of three molecularly different surfactants: lecithin, Tween 20 and sucrose monopalmitate, and their concentration on the stability of curcumin-loaded nanoemulsions, and evaluated their antioxidant capacity. They found that the stability of curcumin in nanoemulsions was not significantly correlated to the concentration of surfactant. They also observed that curcumin loaded nanoemulsions with a concentration of lecithin over 1% showed long-term stability and exhibited higher antioxidant capacity than two other surfactants due to the fact that lecithin contains phosphate ions that are able to form hydrogen bonds with phenolic hydroxyls of curcumin, preventing its autoxidation and hence,

maintaining the antioxidant capacity of curcumin. However, in nanoemulsions containing either Tween 20 or sucrose monopalmitate, antioxidant capacity was negatively correlated to the encapsulation efficiency due to the fact that curcumin was not really encapsulated within the oil phase but retained in the surfactant by hydrogen bonding after nanoemulsions destabilization. Therefore, curcumin exposed to the aqueous media may undergo a spontaneous auto-oxidation degradation and loss of antioxidant capacity.

4.2. Bioaccessibility of curcumin-loaded nanoemulsions

In vitro simulated digestion systems are commonly used to evaluate the bioaccessibility of curcumin encapsulated within emulsion-based delivery systems (Ahmed, Li, McClements, & Xiao, 2012; H. R. Park et al., 2019; Silva et al., 2019). The *in vitro* digestion model consists of three consecutive steps: oral, gastric, and small intestinal phase. To mimic digestion, simulated saliva fluid (SSF) is obtained from mucin and α -amylase at around neutral pH values (e.g. 6.8) for a fixed period of time (e.g.10 min) at a body temperature of 37 °C. Simulated gastric fluid (SGF) involves the addition of salts (e.g. NaCl, KCl, CaCl₂, NaHCO₃), acids (e.g. HCl) and digestive enzymes (e.g. pepsin) at an acidic pH value (e.g. 1.2–4) for a fixed period of time (e.g. 2 h) at 37 °C. Simulated intestinal fluids (SIF) involve the addition of bile extract, pancreatin and electrolyte solution (e.g. NaCl, KCl, CaCl₂) at a neutral to alkaline pH values (e.g. 6.5-7.5) for a fixed period of time (e.g.2 h) at 37 °C (H. R. Park et al., 2019; Sarkar, Goh, Singh, & Singh, 2009). *In vitro* lipid digestion assays have been developed to quantify the release of curcumin (Aditya et al., 2015; Ahmed et al., 2012; H. R. Park et al., 2019; Sari et al., 2015). Lipid digestion products (e.g., free fatty acids) generated by lipolysis of the oil can form various colloid phases (e.g., mixed micelles) that are available to solubilize the released curcumin. The fraction of curcumin release into the mixed micelle phase after lipid digestion can be used to quantify its bioaccessibility (Ahmed et al., 2012). Many studies considering the bioaccessibility of curcumin-loaded nanoemulsions are discussed in the

following section and have been summarized in [Table 2](#).

Many studies show that emulsion-based systems can greatly increase the bioavailability of curcumin within the GIT compared to crystalline curcumin dispersed within water. Aditya et al. (Aditya et al., 2015) encapsulated curcumin and catechin in a water-in-oil-in-water (W/O/W) double emulsion using two-steps emulsification. They reported that encapsulation of curcumin within an emulsion-based system enhanced 4-fold their bioaccessibility (72%) compared to that of freely suspended curcumin (16%), because the presence of mixed micelles available to incorporate curcumin. In a recent work, Park et al. (S. J. Park, Garcia, Shin, & Kim, 2018) prepared Tween 80 - stabilized nanoemulsions and curcuminoids-loaded nanoemulsions developed by combining a liquid lipid (MCT) and solid lipid (glycerol monostearate, GMS). The encapsulated curcumin exhibited a notable increase in bioaccessibility ($75\pm 1.24\%$) compared with curcumin solution ($1.7\pm 0.24\%$). In another work, Zheng et al. (Zheng, Peng, Zhang, & McClements, 2018) prepared curcumin-loaded nanoemulsions using three different methods: the conventional oil-loading method, the heat-driven method, and the pH-driven method. The different curcumin formulations were then subjected to a simulated GIT model consisting of mouth, stomach, and small intestine phases. All three nanoemulsions had fairly similar curcumin bioaccessibility values (74–79%), significantly higher than that of curcumin solution (10%). It suggests that encapsulating curcumin within small lipid particles may be advantageous for improving its absorption from the GIT. Furthermore, bioaccessibility of curcumin in emulsion-based systems is influenced by many factors, including oil composition, droplet size and curcumin-emulsifier interactions. Several researches indicated that the bioaccessibility of curcumin is affected by the type and the amount of carrier oil present in the nanoemulsion- based delivery systems. The nature and physicochemical properties of the free fatty acid, generated by digestion of the oil, are quite different (Ye, Cao, Liu, Cao, & Li, 2018). Long chain fatty acids form mixed micelles more

easily than medium chain fatty acids, and short chain fatty acids produced by lipolysis of the SCT can not form mixed micelles to solubilize and transport curcumin. The mixed micelles formed by long chain fatty acids have a better solubilization capacity because of the large dimensions of the hydrophobic core. Ahmed et al. (Ahmed et al., 2012) examined the influence of triacylglycerol molecular weight on curcumin bioaccessibility. Emulsions containing only short chain triacylglycerols (SCT) within the carrier lipid had only about 1% bioaccessibility. However, utilization of MCT and long chain triacylglycerols (LCT) within the emulsion can greatly increase curcumin bioaccessibility due to the presence of mixed micelles. The bioaccessibility of curcumin was ~40% in the LCT nanoemulsions but ~20% in the MCT nanoemulsions when the concentration of oil in the nanoemulsion was lower than 1.5%. Similarly, Shah et al. (Shah, Zhang, Li, & Li, 2016) observed that there were differences in curcumin bioaccessibility between MCT and LCT nanoemulsions when the oil was almost fully digested. In their study, the bioaccessibility was around 32% in the MCT nanoemulsions but around 65% in the LCT nanoemulsions. The bioaccessibility of curcumin may increase with increasing total lipid content, due to the increase in mixed micelles available to solubilize the curcumin. However, the bioaccessibility may not increase when the amount of lipid is higher than a certain content due to the fact that the lipid phase is not fully digest, which results in an incomplete release of curcumin from the droplets into the mixed micelles phase. For example, Ahmed et al. (Ahmed et al., 2012) prepared an O/W nanoemulsion stabilized by 1 wt.% protein. The bioaccessibility of curcumin increased as the total lipid content increased, while the bioaccessibility of curcumin was similar at 1.5 and 2.0 wt. % lipid when using LCT as the carrier lipid.

Various studies have revealed that the bioaccessibility of curcumin was dependent on the emulsifier type. Emulsifier type has an influence on the curcumin bioaccessibility, by altering the droplet surface area within the digestive tract, or by changing the ability of digestive

enzymes to bind onto the emulsions droplet surface. During the simulated digestion, nanoemulsions show an increase in size due to the addition of digestive enzymes and the change of pH, ionic strength or shear (aggregation, coalescence and flocculation of the oil droplets), leading to a decreased surface area for enzyme interaction (Golding et al., 2011; Hur, Decker, & McClements, 2009). Nanoemulsions stabilized by non-ionic emulsifier are more stable in acidic gastric environments owing to steric repulsions provided by the polyoxyethylene head groups resulting in a slowly increase in the droplets size with a large surface area for the binding of bile salts and lipase (Golding et al., 2011; Pinheiro et al., 2013). For example, Pinheiro et al. (Pinheiro et al., 2013) reported that higher curcumin bioaccessibility during digestion (initial , stomach, duodenum, jejunum, ileum) for nanoemulsions stabilized by Tween 20 (non-ionic, ~16.0% in ileum), as compared to the ones stabilized by dodecyltrimethylammonium bromide (DTAB, cationic, ~1.0% in ileum). The increased bioaccessibility for Tween 20-stabilized nanoemulsions was attributed to the smaller increase in emulsion size (~350 nm) when compared with that of the size of DTAB-stabilized nanoemulsions (~900 nm) during the digestion process. In addition, it has been suggested that the interaction promoted by the strong electrostatic binding between cationic emulsifier and bile salts resulted in the binding of lipase and thus free fatty acid release (Pinheiro et al., 2013). However, with the anionic emulsifier-stabilized emulsion, charged repulsion between anionic emulsifier and anionic components (e.g. bile salts) or free fatty acid could inhibit effective binding of bile salts and thus prevent the binding of lipase (Pinheiro et al., 2013).

Several researches have shown that emulsifier-curcumin interactions can reduce the curcumin bioaccessibility as part of curcumin is not detected in the micelle phase. Pinheiro et al. (Pinheiro, Coimbra, & Vicente, 2016) found that total curcumin bioaccessibility in lactoferrin and lactoferrin/alginate-stabilized nanoemulsions were relatively low (~5%) in jejunum and

ileum. In their work, lactoferrin was responsible for the low bioavailability of curcumin in simulated digestion system. Silva et al. (Silva et al., 2018) observed that lower bioaccessibility values were observed for polyelectrolytes (0.04% chitosan 1st, 0.04% alginate 2nd and 0.02% chitosan 3rd layer) multilayer nanoemulsions ($26.98 \pm 3.99\%$) when compared nanoemulsions ($43.64 \pm 6.36\%$). These results may be explained by the fact that polyelectrolyte layers were efficient in protecting the release of curcumin from the multilayer nanoemulsions, leading to undigested nanosystems able to retain curcumin.

5. Applications of curcumin-loaded nanoemulsions

Curcumin has attracted growing consideration owing to its wide range of beneficial biological and pharmacological activities, such as antioxidant, anti-inflammatory and anticancer activities (Almeida, Sampaio, Bastos, & Villavicencio, 2018; Ghasemi et al., 2019; Güran, Şanlıtürk, Kerküklü, Altundağ, & Süha Yalçın, 2019), but its hydrophobic nature limits its utilization as a nutraceutical in many applications (Huang et al., 2016). Hence, research has been conducted to encapsulate curcumin using delivery systems that can solve these limitations. Compared to curcumin alone, encapsulated curcumin has shown greater biological activity as the delivery system provides sustained release, good stability and enhanced curcumin solubility in aqueous medium (Hashim et al., 2019; Mohammadian, Salami, Momen, Alavi, & Emam-Djomeh, 2019; Sorasitthyanukarn, Muangnoi, Thaweeseest, Rojsitthisak, & Rojsitthisak, 2019).

5.1. Antioxidant activity of curcumin nanoemulsions

Curcumin has been reported to exhibit various antioxidative effects in many cellular and animal models of different diseases (Eybl et al., 2006; Phan et al., 2001). Generally, it exerts an antioxidant activity in a direct or an indirect way by scavenging oxygen free radicals and inducing an antioxidant response, respectively (Antunes, Araújo, Darin, & Bianchi, 2000). In fact, various reports have indicated that curcumin may be a beneficial antioxidative agent, but

its chemistry properties limit its potential as a therapeutic agent in clinical trials. Therefore, researchers focused their attention on the feasibility of using nanotechnology-based systems, such as nanoemulsions, as efficient carriers of curcumin.

Table 3 summarizes some of the recent studies on antioxidant effects of curcumin-loaded nanoemulsions. For instance, Sari et al. (Sari et al., 2015) successfully formulated curcumin-loaded nanoemulsions by ultrasonification using whey protein concentrate-70 and Tween-80 as emulsifiers. The encapsulated curcumin showed a slightly lower DPPH radical scavenging activity as compared to that of unencapsulated curcumin, but the encapsulation not only preserves the antioxidant activity but also increases curcumin stability. In other words, the antioxidant activity of encapsulated curcumin is bio-accessible, i.e., released from the food matrix and solubilized. In another study, Chuacharoen et al. (Chuacharoen & Sabliov, 2019) fabricated three various types of curcumin-nanocarriers including nanosuspensions, nanoparticles and nanoemulsions using lecithin along with Tween 80 as surfactants and MCT as oil phase in nanoemulsions. Curcumin-nanocarriers were added into milk for evaluation of the lipid oxidation and color changes during storage. Antioxidant activity was determined by TABRS (thiobarbituric acid reactive substances) assay, and color of milk was determined by spectrophotometer. The results show that all curcumin-nanocarriers had the capability to inhibit lipid oxidation, which enhanced nutritional quality of milk. On the other hand, nanocurcumin-fortified milk had color changes insignificant from control milk after 5 days. Similarly, Joung et al. (Joung et al., 2016) observed significantly reduced lipid oxidation of milk during storage when using a curcumin-nanoemulsions-fortified milk as compared to control milk and milk containing empty nanoemulsions (without curcumin). These results suggested that curcumin-nanoemulsions have potential applications in the beverage industry because of their antioxidant properties.

5.2. Anti-inflammation activity of curcumin nanoemulsions

Curcumin has been used traditionally as an anti-inflammatory agent. It suppresses the activation of free radical-activated transcription factors, such as nuclear factor κ B (NF- κ B) and activator protein-1 (AP-1), and reduces the generation of pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β) (Chen et al., 2017; Rakariyatham et al., 2019). However, the therapeutic outcome of clinical studies has remained challenging due to its hydrophobic nature. In order to achieve optimum therapeutic effect, nanoemulsions have been proposed as a suitable delivery system in the treatment of inflammation and infections due to their ability to prolong the retention time of curcumin and enable control over the release of incorporated curcumin.

A number of publications have dealt with curcumin nanoemulsions formulations for anti-inflammatory applications. Some effects of curcumin-loaded nanoemulsions on anti-inflammation activity of curcumin are presented in [Table 3](#). For example, Wang et al. (Wang et al., 2008) assessed the anti-inflammation activity comparing the inhibition effect on the edema of mouse ear (12-O-tetradecanoylphorbol-13-acetate (TPA)-induced edema of mouse ears) between curcumin encapsulated in Tween 20-stabilized MCT-carried nanoemulsions and curcumin solution (10% Tween 20 water solution). The oral administration of 1% curcumin solution showed little inhibition effect on TPA-induced edema of mouse ear as Tween 20 could not prevent the fast metabolism of curcumin in mouse body. On the contrary, it was found that 1% curcumin-loaded nanoemulsions had significant inhibition effect on TPA-induced edema of mouse ear (43%~85% reduction) due to the fact that nanoemulsions promoted the absorption of curcumin within the intestine tract. The result suggested that curcumin in nanoemulsions significantly improved the anti-inflammation activity of curcumin. Also, Thomas et al. (Thomas et al., 2017) reported that five different curcumin nanoemulsions with the same quantity of curcumin, stabilized by different ratios of Tween 80 and polyethylene glycol (PEG 400), showed a good *ex-vivo* skin permeation

($75.306 \pm 5.4 \sim 107.1 \pm 5.9 \mu\text{g}/\text{cm}^3/\text{h}$ for flux values) and skin deposition (17.46%~46.07%). In addition, nanoemulsions gels were developed by incorporation of the optimized formulation nanoemulsions (oil: surfactant: distilled water=15:40:45, Labrafac PG: Triacetin=1:1, Tween 80: PEG=2:1) into 2% chitosan at acidic pH conditions. The formulated gel had a good spreadability because of sufficient viscosity (504 ± 21.4 cps) and compatibility to human skin due to neutral pH (6.4 ± 0.121). Moreover, 98% of the formulated gel reached the skin. The nanoemulsions gel had a lower flux ($68.88 \mu\text{g}/\text{cm}^3/\text{h}$) compared to the corresponding nanoemulsions ($76.05 \mu\text{g}/\text{cm}^3/\text{h}$), but it had higher amount of curcumin ($980.75 \pm 88 \mu\text{g}$) retained in the skin compared to the corresponding nanoemulsions ($771.25 \pm 67 \mu\text{g}$). Furthermore, incision wound model rats treated with the nanoemulsions gel showed full wound closure after 12-days treatment whereas the control groups dragged behind significantly. These studies have proved that curcumin-loaded nanoemulsions can be used for improving wound healing as they enhance the bio-accessible anti-inflammation activity of curcumin and possess antioxidant activity to prevent oxidative damage *in vivo*.

5.3. Anti-cancer activity of curcumin nanoemulsions

Anti-cancer activity of curcumin has been extensively investigated on numerous kinds of malignancies, such as breast, prostate, pancreatic and gastric cancers (Liu & Ho, 2018; Teiten, Gaascht, Eifes, Dicato, & Diederich, 2010; Bimonte et al., 2016; Jakubek et al., 2019). Curcumin inhibits transformation, proliferation, suppresses tumors metastasis and induces apoptosis through the regulation of various molecular targets (transcription and growth factors) and its receptors (inflammatory cytokines, protein kinases and other enzymes) (Guan et al., 2017; Rodrigues, Anil Kumar, & Thakur, 2019). However, pharmaceutical significance and therapeutic efficacy of curcumin is limited due to its poor pharmacokinetic properties (poor bioavailability and short biological half-life). To overcome pharmaceutical issues, various

strategies have been employed for effective delivery of curcumin which include nanotechnology-based approaches. Nanoencapsulation based nanoemulsions have the ability to increase the efficacy of curcumin pharmaceutical significance.

Various in vitro and in vivo studies obviously reveal that nanoemulsions can enhance the anticancer efficacy of curcumin. Some studies on application of curcumin nanoemulsions in cancer therapy are illustrated in [Table 3](#). For example, Machado et al. (Machado et al., 2019) in a recent study prepared nanoemulsions stabilized by anionic surfactant poloxamer 188 which showed a high cellular uptake on MCF-7 (human breast adenocarcinoma cell line) and HFF-1 (human foreskin fibroblast cell line) cells, as well as absence of cytotoxicity, thus being classified as an effective and safe drug. They also reported that the use of curcumin-nanoemulsions in photodynamic therapy resulted in a high phototoxic effect, decreasing the proliferation of cells and increasing the reactive oxygen species (ROS) generation in both cell lines. Their study suggested that curcumin nanoemulsions have a great potential to treat breast cancer. Similarly, Guan et al. (Guan et al., 2017) evaluated curcumin loaded nanoemulsions for prostate cancer. Curcumin nanoemulsions can enter the PC-3 cells (human prostatic carcinoma cell line), and exhibit higher cytotoxicity than free curcumin. The nanoemulsions present also a significantly prolonged biological activity and improved therapeutic efficacy compared to free curcumin.

Some other studies reported the anti-cancer efficacy of curcumin nanoemulsions in animal models. For instance, Ganta et al. (Ganta, Devalapally, & Amiji, 2010) designed curcumin and paclitaxel-loaded nanoemulsions for treatment of ovarian adenocarcinoma in tumor-bearing mice. The results revealed that curcumin downregulated the intracellular levels of intestinal P-glycoprotein (Pgp) and cytochrome P450 3A2 (CYP3A2), thereby increasing the

bioavailability of paclitaxel and inhibiting its metabolism. The coadministration of curcumin and paclitaxel in nanoemulsions did not induce any acute toxicity, and showed significant enhanced anti-tumor activity. Guerrero et al. (Guerrero et al., 2018) evaluated curcumin-loaded nanoemulsions for the treatment of recurrent tumor growth and metastasis. The results showed that nanoformulation reduced *in vitro* cell proliferation, increased ROS levels and permitted more persistent intracellular accumulation of curcumin, and prevented migration and invasion of melanoma cells. *In vivo* experiments also showed that curcumin-loaded nanoemulsions prevented melanoma recurrence and lung metastasis post-surgery from remnant cells.

6. Conclusions and future trends

Curcumin is a natural compound with polyphenolic nature. This bioactive ingredient has been proved to possess several functional properties. Research performed to date has highlighted the advantages of curcumin nanoencapsulation on its bioaccessibility and pharmacological activities. This review comprehensively summarizes the main nanoencapsulations techniques. The available scientific investigations indicate that over six nanoemulsions preparation methods are used to encapsulate curcumin, including low-energy method (PIT and PIC), high-energy method (HPH, microfluidization and ultrasonication) and intermediate energy method (membrane emulsification). However, large-scale preparation of curcumin-nanoemulsions, from a pilot scale to industrial exploitation, should gain increasing attention.

Extensive studies have been performed to optimize and design effective nanoemulsion systems with improved physicochemical stability and bioaccessibility. The key factors affecting the stability and bioaccessibility of curcumin in nanoemulsion-based systems are the nature and concentration of emulsifier, oil type and volume fraction and emulsifier-curcumin interactions. LCT nanoemulsions tend to have better bioaccessibility than MCT

nanoemulsions. Additionally, the bioaccessibility of curcumin may increase with increasing total lipid content when the lipid phase is fully digested. Furthermore, emulsifier type has an influence on the curcumin bioaccessibility, by altering the droplet surface area within the digestive tract, or by changing the ability of digestive enzymes to bind onto the emulsions droplet surface. Nevertheless, emulsifier-curcumin interactions can reduce curcumin bioaccessibility.

In addition, this review outlines pharmacological activity of curcumin-loaded nanoemulsions. Pharmacological activity of curcumin-loaded nanoemulsions have been focused on the bioassays in both *in vitro* (cell lines) and *in vivo* (mice and rats). They are advantageous over curcumin solutions for a wide range of applications. Indeed, nanoencapsulation techniques have been commonly applied to enhance the functional properties of curcumin, including antioxidant, anti-inflammation and anti-cancer activities.

According to the applications section of this review, nanoformulations of curcumin will be useful in the near future for different products. However, there is still a need for further studies to give researchers and industries a broad range of deeper information. In particular, further work is needed in areas such as toxicological evaluations and clinical applications of curcumin as a nanomedicine for the prevention and treatment of various diseases or as a nanoadditive in food products. Additionally, to obtain high entrapment efficiency and narrowed particle size distribution, a new preparation technique with medium energy membrane emulsification, could be investigated.

Conflicts of interest

The authors declare that they have no conflict of interest.

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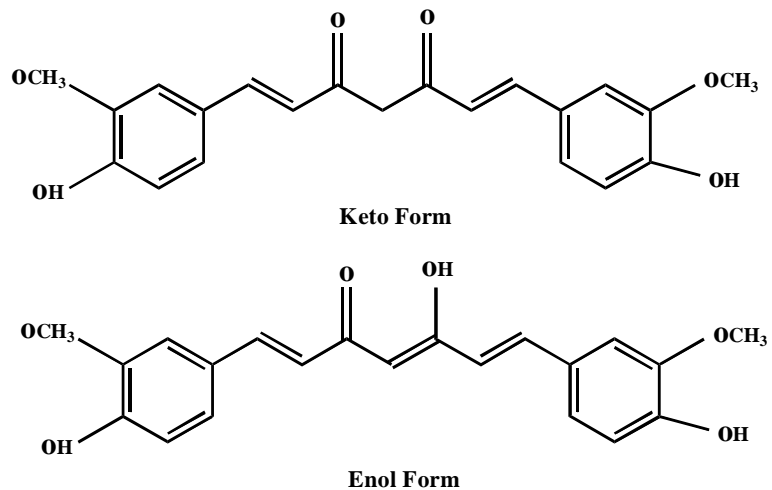


Fig. 1. Structural representation of keto (top) and enol form (bottom) of curcumin.

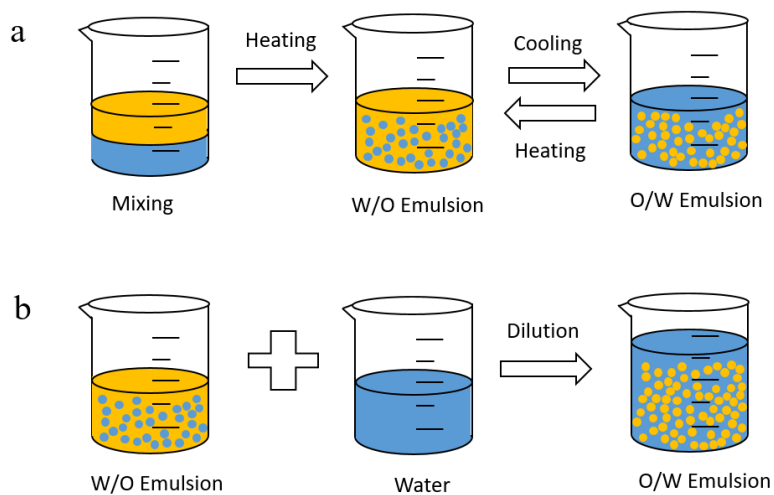


Fig. 2. Schematic illustration of PIT (a) and PIC (b).

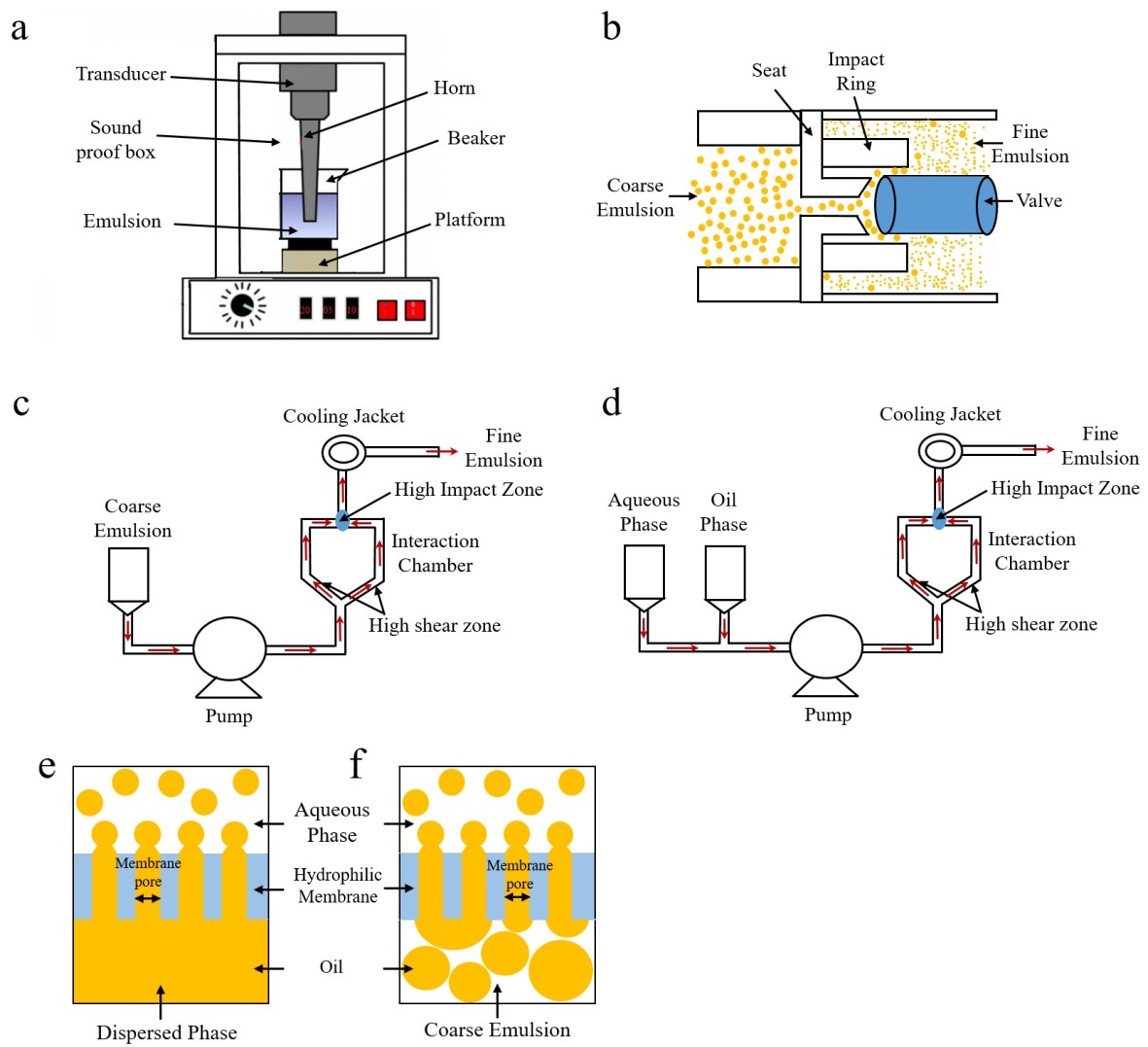


Fig. 3. Schematic illustration of ultrasonication (a), HPH (b), two-step single-channel microfluidization (c) and one-step dual-channel microfluidization (d), DME (e) and PME (f).

Table 1

Summary of the methods of preparation of curcumin-loaded nanoemulsions.

Methods	Surfactant(s) (w/w%)	Oil (w/w%)	Curcumin dispersion method and concentration (w/w%)	Emulsification process	DZ (nm) PDI	ZP (mV)	References
PIT	RH40 (10~20 ^a)	Coconut oil (8.3 ^a)	Magnetic stirring (60 °C, 60 min), then shaken (30 °C, 24 h)/0.008~0.167 ^a	Magnetic stirring (3 temperature cycles 90-60-90-60-90-75°C)	33~78 (PDI ≤ 0.1)	-6.5~2.6	Jintapattanakit et al. (2018)
	Tween 80 (5~40 ^a)	Extra virgin olive (1~9 ^a)	Magnetic stirring (in the dark under nitrogen)/ 0.5 ^a	Magnetic stirring (70-90-20°C)	100-1000	–	Calligaris et al. (2017)
Ultrasonication	Hydroxylated soy lecithin (1.44~14.4 ^b) Purity Gum 2000, Hi-Cap 100 or Purity Gum Ultra (0.5~15 ^a)	MCT, Grapeseed oil, or Olive oil (2~20 ^b)	Curcumin dissolved in ethanol, then oil, evaporation of ethanol/10 ^c	High-speed mixer (6,500 rpm, 4 min), Ultrasonication (130 w and 750 w, 30 min)	≤ 600 (PDI ≤ 0.35)	≤ -50	Páez-Hernández et al. (2019)
	100 or Purity Gum Ultra (0.5~15 ^a) whey protein concentrate-70 (0.5 ^a) and Tween-80 (2 ^a)	MCT (2~14 ^b)	Magnetic stirring (100 °C, 7 min) /1~15 ^c	High-speed mixer (14000 rpm, 2 min), High-intensity sonication (120-1200 w, 1-13 min)	≤ 260 (PDI ≤ 0.2)	≤ -25	Abbas et al. (2014)
		MCT (2 ^a)	-/40 ^c	Magnetic stirring (room temperature), Sonification	141.6 (PDI = 0.27)	-6.9	Sari et al. (2015)
HPH	Polyvinyl alcohol (0.5 ^a) or poloxamer (0.1 ^a)	Glyceryl monooleate (1.4 ^a)	Curcumin dissolved in acetone/4, 8 ^a	Magnetic stirring (7,000 rpm, 2 min), HPH (15,000 psi, 10 cycles)	≤ 400	0~20	Mistry et al. (2012)
	Tween 80 (2 ^a), lecithin (5 ^a), acacia powder (5 ^a), whey protein (5 ^a)	MCT, linseed oil or canola oil (5~30 ^a)	Ultrasonication/12 ^c	High-speed blender (10,000 rpm, 6 min), HPH (60MPa, 3 cycles)	200~4000	-60~0	Ma et al. (2017)
	When protein isolate (1.5 ^a)	MCT (10 ^a)	70 °C/0.1 ^a	Ultra-Turrax homogenizer (5000 rpm, 2 min), HPH (40 bars, 20 cycles)	186 (PDI = 0.124)	-51.9	Silva et al. (2019)
Microfluidization	Tween 80 (0.5~1 ^a)	Palm olein oil (20 ^a)	Curcumin and oil dissolved in ethanol/1 ^a	High-speed homogenizer (7,000 rev/min, 1h), Microfluidizer (350-450 bar, 1-12 cycles)	≤ 270 (PDI ≤ 0.3)	-43~-31	Raviadaran et al. (2018)
	Hydroxylated soy lecithin (1.44~14.4 ^b)	MCT, Grapeseed oil and Olive oil (2~20 ^b)	Curcumin dissolved in ethanol, then oil, evaporation of ethanol/10 ^c	High-speed mixer (6500 rpm, 4 min), Microfluidizer (70 or 140 MPa, 1-10 cycles)	≤ 200 (PDI ≤ 0.38)	≤ -50	Páez-Hernández et al. (2019)
	Tween 20, Lecithin or Sucrose monopalmitate (0.5~2 ^a)	Corn oil (0.5 ^a)	Magnetic stirring (room temperature, 24 h)/0.4 ^a	High-shear homogenizer (11,000 rpm, 2 min), Microfluidizer (150 MPa, 5 cycles)	≤400 (PDI ≤ 0.54)	≤ -37	Artiga-Artigas et al. (2018)

^a w/w%; ^b v/v%; ^c mg mL⁻¹.

Abbreviations: DZ, droplet size; ZP, zeta potential; PDI, polydispersity index.

Table 2

Composition and formation of nanoemulsions for delivery of curcumin.

Surfactant(s) (w/w%)	Oil (w/w%)	Curcumin dispersion method and concentration (w/w%)	Emulsification process	DZ (nm) PDI	ZP (mV)	References
Tween 80 (1% ^a)	Corn oil (1 ^a)	Curcumin dissolved in stock emulsions (85 °C, 2 h)/3 ^c	High shear mixer (2 min), HPH (12,000 psi, 5 cycles)	270 (PDI ≤ 0.38)	-20.3(pH 7) +0.2(pH 3)	Zheng et al. (2017)
Soy soluble polysaccharide:casein = 1:1 (20 ^c)	MCT : Vitamin E = 1:1 (16.7 ^b)	Curcumin dissolved in Vitamin E and MCT (-)/1.7 ^c	Homogenizer (10,000 rpm, 1 min), HPH (800 bar, 4 min)	300~500	-50~10	Xu et al. (2017)
Gun arabic, saponins, Tween 80 and caseinate (0.5~10 ^a)	MCT(9 ^a)	Magnetic stirring (60 °C, 2 h), then sonicated (20 min) /0.1 ^a	High-speed blender (2 min), Microfluidization (12,000 psi, 5 cycles)	~2000	-65.3~-2.2	Kharat et al. (2018)
Tween 20, Lecithin or Sucrose monopalmitate (0.5~2 ^a)	Corn oil (0.5 ^a)	Magnetic stirring (room temperature, 24 h)/0.4 ^a	High-shear homogenizer (11,000 rpm, 2 min), Microfluidization (150 MPa, 5 cycles)	≤400 (PDI ≤ 0.54)	≤-37	Artiga-Artigas et al. (2018)
Polyglycerol polyricinoleate (0.6 ^a) and Tween 80 (1 ^a)	Olive oil (18.75 ^a)	Magnetic stirring (15 min)/0.1 ^d	Magnetic stirrer(1500 rpm, 2 min), Sonication(20 kHz, 4 min) for W/O nanoemulsions, and then added to the secondary water phase using the same process	<590	~-20	Aditya et al. (2015)
Glycerol monostearate (3 ^a) and Tween 80 (1~20 ^a)	MCT(-)	Magnetic stirring (70°C, 2 h)/0.1 ^a	High-speed homogenization (5000 rpm, 1 min), Sonification (1~9min)	200~500 (0.2 < PDI < 0.8)	-15~-25	Park et al. (2018)
Quillaja saponin (1 ^a)	Corn oil (5 ^a)	Incubation (60°C, 2 h) or curcumin dissolved in stock emulsions (100 °C, 15 min or pH 12.5)/0.015 ^a	High-speed blender (2 min), HPH (12,000 psi, 5 cycles)	170~200	~-45	Zheng et al. (2018)
β-lactoglobulin (1 ^a)	Corn oil, MCT or Tributyrin (10 ^a)	Magnetic stirring (60°C, 10 min), sonication (20 min)/0.15 ^a	High-speed blender (2 min), HPH (9000 psi, 5 cycles)	174, 181, 1981 and 182 (0.13<PDI<0.75)	-	Ahmed et al. (2012)
Span80:Tween80=1.5:8.5 (10 ^a)	MCT or LCT(5 ^a)	Magnetic stirring (overnight)/0.1 ^a	Magnetic string (room temperature, 15 min)	< 200	-4.26 or -12.84	Shah et al. (2016)
Tween 20, SDS or DTAB (0.5 ^a)	Corn oil (5 ^a)	-/0.1 ^a	High-speed blender (2 min), Microfluidization (20,000 psi, 5 cycles)	124, 152 or 119 (PDI = 0.42, 0.19, 0.22)	-1.03, -92.86 or -89.42	Pinheiro et al. (2013)
Lactoferrin (2 ^a) or lactoferrin (2 ^a) /alginate (0.2 ^a)	Corn oil (5 ^a)	-/0.1 ^a	High-speed homogenization (2 min), HPH (20,000 psi, 20 cycles)	<500	27.47 or~-30	Pinheiro et al. (2016)
SDS (1 ^a) or chitosan (0.06 ^a) / alginate (0.02 ^a) / SDS(1 ^a)	MCT(10 ^b)	(90°C, 30 min)/0.1 ^a	High-speed homogenization (2 min), HPH (15,000 psi, 20 cycles)	80 (PDI = 0.177) or 130 (PDI = 0.237)	-65.8 or 10.4	Sliva et al. (2018)

^a w/w%; ^b v/v%; ^c mg mL⁻¹; ^d w/v%.

Abbreviations: DZ, droplet size; ZP, zeta potential; PDI, polydispersity index.

Table 3

Examples of studies considering applications of curcumin nanoformulations.

Application	Methods of preparation	Study design	Study outcome	References
Anti-oxidant	<ul style="list-style-type: none"> Prepared by magnetic stirring and sonification using MCT as oil, Tween 80 as surfactant and WPC-70 as emulsifier 	The total antioxidant activity was determined by DPPH, and the GIT digest was analyzed for release of curcumin.	The encapsulation not only preserved the antioxidant activity but also slowed down the release of curcumin	Sari et al. (2015)
	<ul style="list-style-type: none"> Prepared by HPH using MCT as oil, Tween 80 and lecithin as surfactants Prepared by high-speed homogenization and HPH using MCT as oil, Tween 20 as emulsifier 	<p>The stability of curcumin-nanocarriers was addressed and applied to milk systems.</p> <p>Curcumin nanoemulsions were developed and applied to commercial milk systems.</p>	<p>Curcumin-nanocarriers protected curcumin against degradation and inhibited lipid oxidation.</p> <p>Curcumin nanoemulsions were significantly effective to reduce lipid oxidation of milk during storage.</p>	<p>Chuacharoen et al. (2019)</p> <p>Joung et al. (2016)</p>
Anti-inflammatory	<ul style="list-style-type: none"> Prepared by high-speed homogenization and HPH using MCT as oil and Tween 20 as emulsifier Prepared using Labrafac PG + Triacetin as oil, Tween 80 as a surfactant and polyethylene glycol (PEG 400) as a co-surfactant. 	<p>The anti-inflammatory activity of curcumin nanoemulsions was studied in a mouse ear inflammation model.</p> <p><i>Ex-vivo</i> permeation and deposition studies were performed through rat skin, and wound-healing activity was performed by incision wound model in wistar rats.</p>	<p>Curcumin nanoemulsions showed improved inhibition on the edema of mouse ear, and such activity was further enhanced when emulsions droplet sizes were reduced to below 100 nm.</p> <p>Nanoemulsion can be used for loading curcumin for the treatment of wound healing.</p>	<p>Wang et al. (2008)</p> <p>Thomas et al. (2017)</p>
Anti-cancer	<ul style="list-style-type: none"> Prepared by spontaneous nanoemulsification method using MCT and natural soy phospholipids as oil, and poloxamer 188 as surfactant Prepared by self-microemulsifying method using MCT as oil, cremophor RH 40 as surfactant and glycerol as co-surfactant. 	<p>The action of curcumin nanoemulsion used as a photosensitizing agent in photodynamic therapy in an in vitro breast cancer model, MCF-7 cells was analyzed.</p> <p>Curcumin nanoemulsions and curumin against prostate cancer cells (PC-3 cell) was evaluated.</p>	<p>Curcumin-nanoemulsion had phototoxic effects, significantly decreased the proliferation of MCF-7 cells and stimulating the ROS production, demonstrating great potential for treatment of breast cancer.</p> <p>Curcumin nanoemulsions exhibited an increased cytotoxicity and cell uptake, a better therapeutic efficacy than free curcumin. It can be used as an effective drug delivery system to enhance the anticancer effect.</p>	<p>Machado et al. (2019)</p> <p>Guan et al. (2017)</p>
	<ul style="list-style-type: none"> Prepared by ultrasonication using omega-3 fatty acid-rich flax-seed oil as oil, egg yolk lecithin and deoxycholic acid as surfactants 	The effect of curcumin in oral bioavailability and therapeutic efficacy of paclitaxel administered in nanoemulsion to SKOV3 tumor-bearing nu/nu mice was evaluated.	Paclitaxel administered in nanoemulsion to curcumin pretreated mice did not induce any acute toxicity. The combination could improve oral bioavailability and therapeutic efficacy in ovarian adenocarcinoma.	Ganta et al. (2010)
	<ul style="list-style-type: none"> Prepared by spontaneous nanoemulsification method using 	The tototoxicity of curcumin nanoemulsions in different cell lines was determined, and the effect	Nanoformulation increased intracellular curcumin accumulation and ROS formation, while preventing	Guerrero et al. (2018)

Miglyol 812 as oil, Epikuron 145 V as surfactants

on preventing post-surgery tumor reoccurrence and metastasis in C57BL/6 mice was evaluated.

cell-migration and invasion in melanoma cells. It also prevent reincident tumor growth and spontaneous lung metastasis in mice.
