LWT - Food Science and Technology 92 (2018) 92–100

Contents lists available at ScienceDirect

LWT - Food Science and Technology

journal homepage: www.elsevier.com/locate/lwt

Synthesis of nano curcumin using black pepper oil by O/W Nanoemulsion Technique and investigation of their biological activities

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ARTICLE INFO

Keywords:
Curcumin
Nanoemulsion
Black pepper
Tween
Antioxidant activity

ABSTRACT

Curcumin is an important biologically active polyphenolic compound that has been found to contain the ability of a wide range of beneficial biological activities. The aim of this study was to develop a method for the preparation of curcumin nanoparticles (Nano-CUR) with a view to improve its aqueous-phase solubility and examine the effect on its biological properties. Nano-CUR were prepared in black pepper oil (BP oil) as an oil phase and Tween 80 as the surfactant. Nano-CUR was prepared by a modified microemulsion technique and was found to have a narrow particle size distribution in the ranges of 8–26 nm. Nano-CUR was obtained with a spherical shape and mean particle size of 15.7 ± 3.55 nm when the following optimal conditions were adopted as water/oil (5:1) and oil/surfactant (1:9). Unlike curcumin (bulk), Nano-CUR is readily dispersed in aqueous media. The FTIR spectrum indices can be used in order to differentiate nano and non-nano emulsion solutions. Antioxidant activity tests were applied to the Emulsion components, Nano-CUR, and also to Tween 80 + BP oil. Results demonstrated that Nano-CUR has maximum antioxidant activity. *In vitro* cytotoxicity effect of Nano-CUR was also investigated, which was detected in the treated Neuro2A cells to be up to 15.6 μg/mL.

1. Introduction

Curcumin, [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dion], is an important biologically active polyphenolic compound that is extracted from turmeric (Fig. 1) (Basniwal, Buttar, Jain, & Jain, 2011). The use of curcumin in different fields is limited due to its low water solubility and poor bioavailability in physiological media (Rai, Pandit, Gaikwad, Yadav, & Gade, 2015). In recent years, many approaches have indicated on the fact that water solubility and bioavailability of curcumin is significantly improved by reducing its particle size down to nanoscale (Basniwal et al., 2011). Different methods are being developed to produce nanoparticles of curcumin (Nano-CUR) with high solubility, bioavailability, and activity such as nano-precipitation (Arunachalam et al., 2010), spray drying (Ravichandran, 2013), microemulsion (Kumar & Senthil, 2011), excipient emulsions (Zou et al., 2015), solid/oil/water emulsion (Mukerjee & Vishwanatha, 2009), ultrasonic-assisted (Zheng et al., 2010), Fessi (Moorthi, Krishnan, Manavalan, & Kathiresan, 2012), and nanoemulsion (Ahmed, Li, McClements, & Xiao, 2012) methods. Nanoemulsion procedure has been receiving increased attention in the last decade since it fulfills vital requirements such as considering "***green chemistry***" rules, facile process, high efficiency, low price, usage of ecofriendly materials, and low laboratorial requirements. The oil-in-water (O/W) emulsion technique can be used as a nanoemulsion method to prepare Nano-CUR with unique and improved properties e.g., high solubility, bioavailability, antioxidant activity, and etc. (Rachmawati, Yee, & Rahma, 2014). In this method, lipophilic bioactive components can be produced and solubilized within the oil phase, and then be homogenized in an aqueous phase that contains a water-soluble emulsifier. The O/W emulsion method is physico-chemically sensitive since the size of nanoparticles (Droplets; < 100 nm) is severely dependent on the chemical composition that is used, as well as the physical condition (Homogenization). The nanoemulsions that are produced by O/W emulsion method have displayed higher stability, while they often seem to have different physicochemical, biological, and medicinal properties in comparison with conventional emulsions (Sonneville-Aubrun, Simonnet, & L'alloret, 2004).

In the present study, we report a modified O/W emulsion method to

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https://doi.org/10.1016/j.lwt.2018.02.023
Received 26 November 2017; Received in revised form 20 January 2018; Accepted 9 February 2018
Available online 10 February 2018
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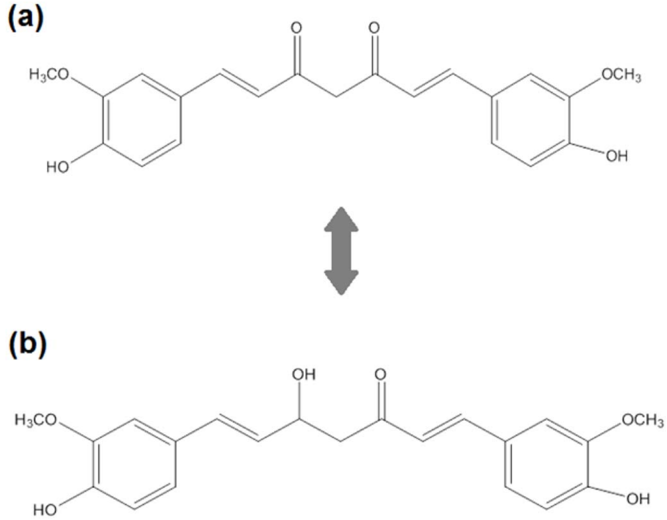

Fig. 1. Different forms of curcumin molecular structures; (a) keto form, and (b) enol form.

prepare Nano-CUR by utilizing black pepper (*Piper nigrum* L.) oil (BP oil) as a suitable oil phase due to its unique properties and health benefits such as digestive, carminative, diaphoretic, antispasmodic, anti-rheumatic, antimicrobial, and antioxidant activities (Bakkali, Averbeck, Averbeck, & Idaomar, 2008; Polovka & Suhaj, 2010). The optimization of synthetic conditions, investigation the synergistic effect of antioxidant activity of curcumin and BP oil, and cytotoxicity effects were also investigated. Moreover, we have used The FTIR spectrum in order to detect nano and non-nano emulsion solutions.

2. Materials and methods

2.1. Materials

Curcumin (> 99%, Merck, Darmstadt, Germany), Tween® 80 ($C_{64}H_{124}O_{26}$, Merck, Germany), BP oil extract (Golsorkh Exir Co., Iran), MTT (3-[4, 5-dimethylthiazol-2-yl]-2, 5-diphenyl tetrazolium bromide, Sigma-Aldrich, 98%, USA), DPPH (2, 2-diphenyl-1-picrylhydrazyl, 98%, Sigma-Aldrich, USA), DMSO (Dimethyl sulfoxide, 99.9%, Sigma-Aldrich, USA), Dulbecco's Modified Eagle Medium (DMEM, Invitrogen, USA), and ethanol (96%, Merck, Germany) were purchased and used without any further purification. Deionized water was utilized in all of the experiments.

2.2. Preparation of Nano-Curcumin (Nano-CUR)

During the preparation of Nano-CUR via oil-in-water (O/W) emulsion method, the oil phase (BP oil) and surfactant (Tween 80) were mixed (by ratio of 1:9 w/w) under continuously stirring for 15 min to form the oily phase. 100 mg of the initial curcumin was added into the oily phase and the mixture was stirred under magnetic stirrer at the speed of 500 rpm for 2 h, in room temperature. Then, the mixture was placed in a sonicator bath (Sonorex Digitec, Model: Andelin; 35 kHz, Germany) for a period of 1 h to obtain a clear yellow homogeneous oily solution. Subsequently, the final nanoemulsion was formed by adding deionized water to the oily phase (Ratio 5:1 w/w) and preceded with stirring at 500 rpm for 30 min. Additionally, in this work, different ratio (w/w) of oil and surfactant were employed, e.g., 0.5:9.5, 1.0:9.0, 1.5:8.5, and 2.0:8.0, respectively, to optimize the size of the prepared Nano-CUR.

2.3. Nano-CUR characterization

2.3.1. Particle size distribution and zeta potential

Particle size distributions and zeta potential of Nano-CUR was carried out by a dynamic light scattering (DLS) instrument (Zetasizer Nano ZS, Malvern Instruments, Malvern, UK). To avoid multiple scattering effects, samples were diluted through the use of deionized water as an appropriate before the particle size and zeta potential measurements, while each individual measurement had an average of 13 runs. All of the measurements were applied at room temperature.

2.3.2. Field emission scanning electron microscopy (FE-SEM)

The surface morphology of Nano-CUR (Freeze dried powder) was observed via a MIRA model of field emission scanning electron microscopy (FE-SEM, Tescan Mira 3, Czech Republic) at an accelerating voltage of 20 kV. The samples were dropped and dried on a metallic substrate and were coated with gold in an ion sputter under vacuum for 180 s before the observation.

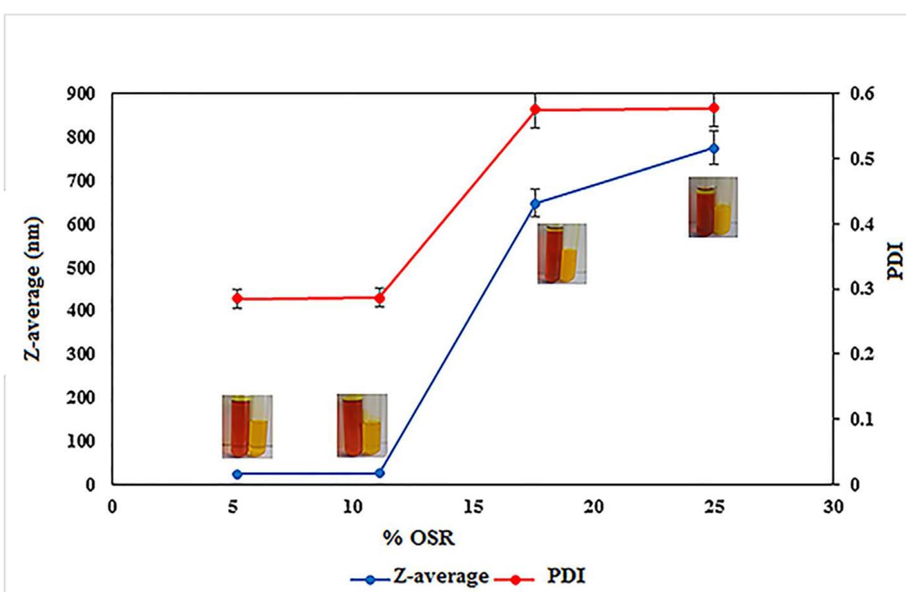

Fig. 2. Effect of oil composition on mean diameter of nanoparticles and their polydispersity index at different OSR. Data were shown as mean diameter ± S.D. and mean PDI ± S.D. (n = 3).