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In vivo evaluation of a self-nanoemulsifying drug delivery system for curcumin

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ABSTRACT

Curcumin has attracted particular attention in recent years due to its great variety of beneficial biological and pharmacological activities. However, its efficacy has been limited due to its low bioavailability, and this limitation can be overcome by novel drug delivery systems. Self-nanoemulsifying drug delivery system (SNEDDS) is a novel route to improve oral bioavailability of lipophilic drugs. SNEDDS spontaneously forms fine oil-in-water nanoemulsion by mild agitation.

An optimal formula for a SNEDDS comprised ethyl oleate:tween 80:PEG 600 (50:40:10% w/w) with 11.2-nm uniform droplets was developed for curcumin delivery. The SNEDDS was characterized and its loading properties for curcumin were orally evaluated in rat. The results showed a significant increment of 3.95 times in C_{max}, and the curcumin bioavailability was enhanced by 194.2%, compared to the curcumin suspension in water. The development of the SNEDDS formulation had a great potential as a possible alternative for curcumin administration.

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1. Introduction

Curcumin, 1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6 heptadien-3,5,dione, is a yellow colored phenolic substance extracted from the spice herb Curcuma longa [1]. It has attracted particular attentions in recent years due to its broad spectrum of beneficial biological and pharmacological activities, such as anti-inflammatory [2], anti-oxidant [3], anti-microbial [4], anti-tumor [5], anti-coagulant [6], anti-virus [7] properties. Moreover, curcumin has been shown to have the potential of slowing the progress of Alzheimer's disease [8] and of delaying the onset of its seizures [9]. It also inhibits the formation of brain tumor [10]. Curcumin is a safe, non-toxic and effective alternative for many new drugs [11].

Nevertheless, the majority of the orally administrated curcumin is extracted in the feces and urine, and a few amounts are detected in blood plasma [8]. Although 10 or 12 g/mL of orally administered curcumin in humans leads to a serum curcumin level of ~50 ng/mL, it is lower than a value to achieve curcumin therapeutic effects [12]. The low bioavailability of curcumin is due to its low water solubility [8], instability in low pH values, and resulted in difficult absorption and limited clinical use [13]. At the same time, after oral curcumin dosing, it is rapidly metabolized in the intestine [8]. In order to overcome these limitations, numerous methods have been suggested to improve the curcumin bioavailability [2,14].

Nanomaterials have a high surface area and surface-to-volume ratio causing increasing in the particle surface energy, which can render them into more biological activity [15–20]. Different nanomaterials have been employed in nanomedicine [16–20]. As for nanovehicles for increment in the drugs' solubility, lipid nanoemulsion formulations, and particularly, the self-nanoemulsifying drug delivery system (SNEDDS) has been considered as an ideal alterative for enhanced the oral bioavailability of poorly water-soluble drugs [21]. SNEDDS is an isotropic mixture consisting of oil, surfactant and cosurfactant, which can spontaneously form a fine oil-in-water nanoemulsion with gentle agitation in water [22]. In human, the digestive motility of the stomach and intestine provides the agitation required for self-emulsification *in vivo* [23]. SNEDDS has received particular attention due to its advantage, e.g. reduction in dose [24], protection of drug from the enzymes of the gastrointestinal tract

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[25], reduction of the first-pass effect [26], reduction of side effects [27], controlled and sustained delivery of drugs [28], minimizing gastric irritation [29], increasing maximum concentration (C_{max}) and area under the curve (AUC), and reduction of maximum concentration (T_{max}) [30].

There are reports on the increment in the bioavailability of some poorly water-soluble drugs using SNEDDS such as cilostazol [31], rosuvastatin calcium [32], irbesartan [33], telmisartan [34], cyclosporine [35] and coenzyme Q10 [36]. However, based on our knowledge, enhancement in the curcumin bioavailability using SNEDDS has not been approached, yet. In the present study, a SNEDDS comprising ethyl oleate, tween 80 and polyethylene glycol (PEG) 600 for curcumin was design, characterized, and evaluated *in vivo*.

2. Materials and methods

2.1. Materials

Curcumin and ethyl oleate were bought from Merck (Germany). PEG 600, tween 80, chloroform and absolute ethanol were purchased from Scharlau (Spain). All chemical were of reagent grade. Methanol and glacial acetic acid (HPLC grade) were obtained from Sigma (USA).

2.2. Solubility study and screening of the SNEDDS components

The most important criterion for the screening of components is the solubility of curcumin in oil, surfactant and cosurfactant. Therefore, the solubility of curcumin in ethyl oleate, tween 80 and PEG 600 was determined. 500 μL of these liquids was added to each vial containing an excess amount of curcumin (50 mg) and shaken at ambient temperature for at least 24 h. Then, the vials were centrifuged at 15000 rpm for 20 min in a sealed micro-centrifuge (Eppendorf 5424, Germany) to remove the undissolved curcumin. The supernatants were collected and stored at room temperature. A UV–vis spectrophotometer (Rayleigh UV-2100, China) was employed for determination of the curcumin concentration in the supernatants. The absorption coefficients for curcumin in each liquid were separately obtained by recording the absorbance values of standard curcumin solutions. The solubility values were expressed as mean ± standard deviation.

2.3. Construction of ternary phase diagram

Ternary phase diagram was constructed in order to obtain the construction range of the components that can form self-nano-emulsion upon dilution. Ethyl oleate, tween 80 and PEG 600 were selected as oil, surfactant and cosurfactant, respectively.

Ternary phase diagram was constructed by using a conventional titration technique. Briefly, appropriate amounts of surfactant and cosurfactant were taken in different stoppered test tubes. The ingredients were mixed using a magnetic stirrer until the solution was clear. Oil was then added drop-by-drop to each mixture under proper magnetic stirring at room temperature until the mixture became turbid at a certain point. The amounts of the components were converted to weight per weight percent before constructing the phase diagram. The shaded areas enclosed in the triangle represent the biphasic regain.

2.4. Optimization of SNEDDS formula from the ternary phase diagram

Four different SNEDDS formulations were prepared by selecting the concentrations of oil, surfactant and cosurfactant from single-phase region of the ternary phase diagram denoted as F1 to F4 (Table 1). The best formulation was selected based on the minimum droplet size.

2.5. Preparation of curcumin loaded SNEDDS

Curcumin was firstly dissolved in PEG 600 in a glass vial and the dispersion was gently shaken at for 10 min until perfect dissolution. Then, the required amount of ethyl oleate and tween 80 was added and shaking continued for 5 min. The curcumin loaded SNEDDS were formed following 1:10 dilution with distilled water. These mixtures were stored at room temperature for further studies. A blank SNEDDS formulation was also prepared by the same method without using curcumin.

2.6. Determination of curcumin loading capacity

10 mg curcumin was loaded into 3 mL of SNEDDS as mentioned above followed by liquid-liquid extraction. To the SNEDDS, 1 mL chloroform was added and then shaken for 5 min. The organic layer was then separated and its curcumin content was quantified by HPLC (Waters, USA).

2.7. HPLC analyses

The chromatographic separations were achieved using C18 column (Eurospher, Germany) with 250 mm × 4.6 mm and particle size of 5 μm coupled with a UV–vis detector. The mobile phase was made of a mixture of methanol and water (73:27, v/v) containing 3.6% glacial acetic acid at a flow rate of 1 mL/min [11], and the run time was 7 min. The mobile phase was filtered through a 0.22 μm Millipore membrane filter and degassed by a sonicator (Wise clean, Germany) for 5 min before use. A 60 μL volume was injected into the system and the eluent was monitored at 428 nm. The retention time of curcumin was practically obtained as 4.16 ± 0.23 min in the working conditions in the present study.

From a calibration curve constructed for the curcumin analysis, the concentration of curcumin in the samples was determined. Standard solutions of curcumin were prepared in the mobile phase as a serial concentration in a range of 0.004–1 mg/mL. All data were expressed as mean ± standard deviation.

2.8. Determination of droplet size of SNEDDS and morphological characterizations

SNEDDS formulations (F1-F4, 200 μL) were dispersed in 2 mL distilled water under gentle agitation. The droplet size was measured using particle size analyzer (Scatterscope, Qudix, South Korea). The selected formulation of SNEDDS (F2) was diluted 200 times with distilled water and then mixed by gentle shaking. One drop of the diluted sample was deposited and stained with osmium tetroxide. Field emission scanning electron microscopy (FESEM) images from this sample were recorded (TESCAN Mira 3-XMU, Czech Republic).

Table 1
Compositions of various formulations presented in the phase diagram.

Composition (w/w%)	Ethyl oleate	Tween 80	PEG 600
F1	15	30	55
F2	50	40	10
F3	20	50	30
F4	20	40	40

2.9. *In vitro drug release*

Curcumin release from a SNEDDS containing 16.5 mg curcumin was carried out by dialysis method. 5.5 mL of curcumin loaded SNEDDS was dialyzed by a dialysis tube (12000 MWCO) against 25 mL release medium containing an ethanol/water 70:30 (v/v) mixture with stirring at 100 rpm. After time intervals of 0.5, 1, 2, 3, 5, and 8 h, 1 mL of the release medium was withdrawn and replaced by an equal volume of fresh one. The samples were then analyzed by HPLC according to the procedure described above. Similar experiments were performed to determine and compare the curcumin release from a curcumin suspension with the same quantity. All experiments were performed in triplicate.

2.10. *Stability*

The physical stability of SNEDDS was visually determined by monitoring the time-dependent change in the phase separation of the SNEDDS formulation. The SNEDDS formulation and curcumin loaded SNEDDS formulation were kept at room temperature for at least 30 days.

2.11. *In vivo studies*

All animal studies were approved by the local ethics committee at the Shiraz University of Medical Sciences (NO: 10006). Additionally, efforts were made to minimize animal suffering and to use only the number of animals necessary to produce reliable scientific data.

Male Sprague-Dawley rats (weight of 250–300 g) were received from the center of comparative and experimental medical at Shiraz University of Medical Sciences. The rats were housed under standard laboratory conditions at 25 ± 2 °C, 55 ± 5% relative humidity and with a controlled 12 h light-dark cycles, before the experiments. Rats were starved for 12 h prior to drug dosing with free access to water ad libitum. They were divided randomly into two groups with six animals in each group. Each group was either administered oral curcumin aqueous suspension (control group) and curcumin loaded SNEDDS (test group) at the same does of 100 mg/kg body weight. Oral suspension of curcumin was prepared by suspending curcumin into distilled water with a concentration of 10 mg/mL.

Each formulation was administered to the rats by oral gavage using an animal feeding needle. Then, the rats were anaesthetized in an ether-saturated chamber. Blood samples (0.5 mL) were collected via heart puncture at 20, 40, 60, 90, 120, 240, 360, 480 and 600 min after oral administration and transferred to microcentrifuge tubes. Blood samples were centrifuged at 3500 rpm for 20 min. The supernatant plasma fraction was transferred to clean tubes and stored at −20 °C.

2.12. *Sample preparation*

Methanol was added to the plasma samples to precipitate the plasma proteins. The samples were then vortexed and centrifuged at 20000 rpm for 10 min. The supernatant was collected for curcumin analysis by HPLC.

2.13. *Data analysis*

The values of C_{max} and T_{max} were directly determined from concentration versus time curves based on the non-compartment model. The values of AUC for the plasma concentrations versus time curves were estimated by the trapezoidal rule. The oral bioavailabilities were obtained using the following equation:

Oral bioavailability (%) = [AUC (test)/AUC (control)] × [Dose (control)/Dose (test)]

Statistical analyses were done using SPSS software, version 21. A p-value of less than 0.05 was considered as statistically significant.

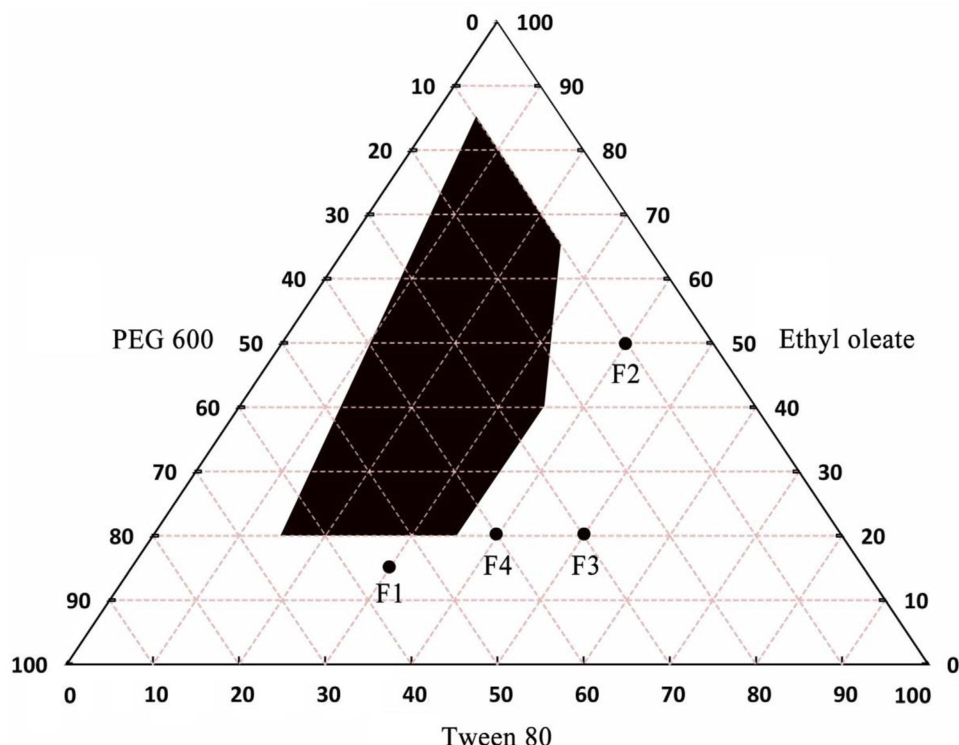


Fig. 1. A ternary phase diagram of the system containing ethyl oleate, tween 80 and PEG 600. Selected formulations were indicated on the diagram.

Table 2
Droplet size analysis for F1-F4, and curcumin loaded F1-F4 formulations.

Formulation	Droplet size, D10-D90 (nm)	Median size (nm)
F1	16.8 nm-42.2 nm	26.4
F1/curcumin	42.2 nm–108 nm	67.4
F2	7.00 nm-17.9 nm	11.2
F2/curcumin	4.31 nm-10.8 nm	6.9
F3	9.36 nm-23.5 nm	14.7
F3/curcumin	10.7 nm-26.8 nm	17.1
F4	16 nm–40 nm	25.6
F4/curcumin	43.5 nm/111 nm	69.6

3. Results and discussion

To select the components of the SNEDDS, the following criteria were noticed. i) Safety is the main determining factor in choosing the components. Nonionic surfactants are less toxic than ionic ones. On the other hand, the value of hydrophilic-lipophilic balance (HLB) for a surfactant to form oil in water nanoemulsion should be greater than 10 [37]. In the present study, tween 80 had a HLB value of 15. ii) The components should be able to achieve small and uniform droplet size. iii) Solubility of curcumin in the components. The solubility of curcumin in the oil, surfactant and cosurfactant was determined (Supplementary material S1). The solubility of curcumin was found to be highest in PEG 600 (39.2 ± 0.1 mg/mL) as compared to tween 80 and ethyl oleate. iv) Formation of a single phase by the components is critical, and upon addition of water, a stable nanoemulsion should be formed. Ternary phase diagram is plotted in order to identify self-nanoemulsify regions and selected suitable range of components for forming fine nanoemulsion. Within these regions, self-nano-emulsifying system requires minimum free energy; hence, emulsification process is thermodynamically spontaneous. The ternary phase diagram of the system containing ethyl oleate, tween 80 and PEG 600 is shown in Fig. 1. The shaded regions represent the biphasic region, and the others represent mono-phasic system. Within this area, the formed nanoemulsion was clear, isotropic and transparent. Different formulations were selected from this region, and shown in Fig. 1, and the components are presented in Table 1. For these formulations, the droplet sizes of SNEDDS without and with curcumin loading were measured by a particle size analyzer (Supplementary material S2) and the results are summarized in Table 2. Based on these results, the formulation containing ethyl oleate:tween 80:PEG 600 with a weight ratio of 50:40:10 (F2) had the lowest droplet size and narrow size distribution, and was selected for further studies.

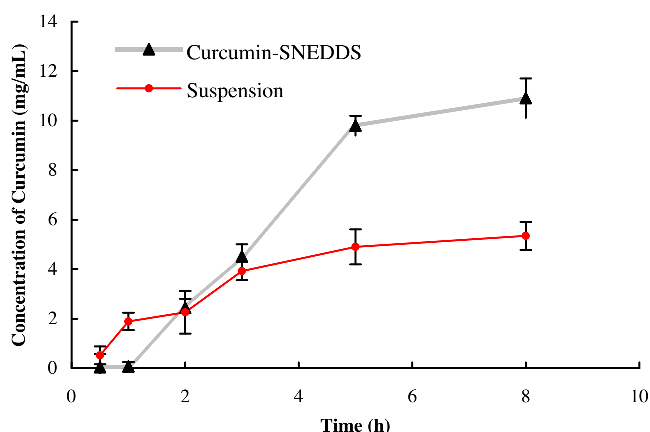
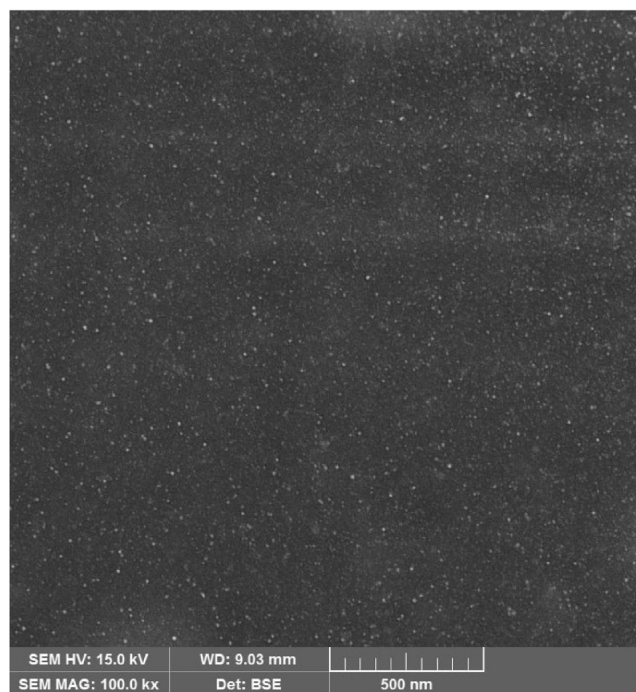


Fig. 2. *In vitro* curcumin release profiles for curcumin loaded SNEDDS and curcumin suspension.

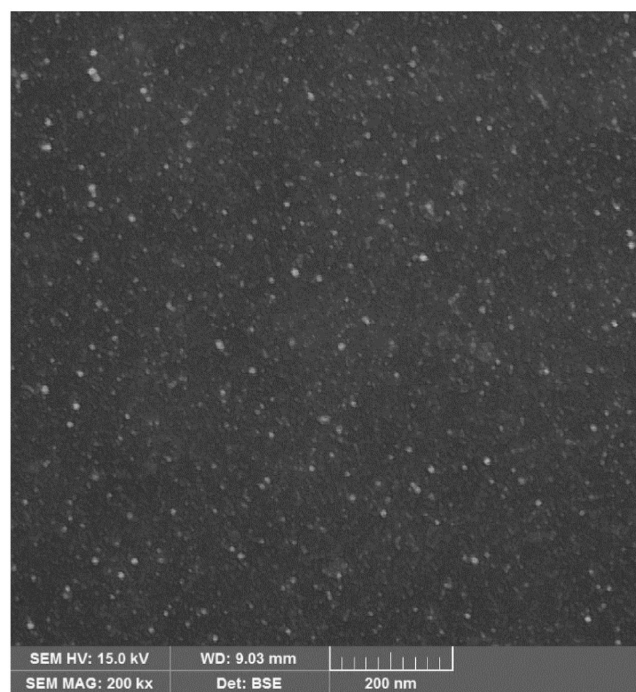
As to the stability of SNEDDS, no phase separation or precipitation for F2 formulation was observed for both the blank and curcumin loaded nanoemulsions.

The curcumin content in the curcumin loaded SNEDDS was determined by HPLC after extraction in chloroform and obtained as 23 ± 5%.

As for investigate the curcumin release, *in vitro* release patterns for both curcumin loaded SNEDDS and its aqueous suspension were measured and are presented in Fig. 2. The results indicated that the curcumin release from SNEDDS was initially slower than



(A)



(B)

Fig. 3. FESEM images of the curcumin loaded SNEDDS at different magnifications.

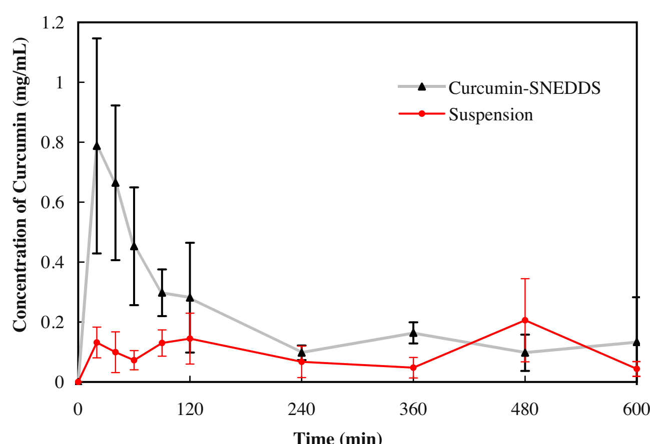


Fig. 4. Time profiles of the mean concentrations of curcumin in plasma samples after oral administration of curcumin loaded SNEDDS and the curcumin suspension at a dose of 100 mg/kg.

Table 3
Pharmacokinetic parameters obtained after oral administered of curcumin loaded SNEDDS and the curcumin suspension.

Parameter	Suspension	SNEDDS
C_{max} (mg/mL)	0.2 ± 0.14	0.79 ± 0.36
T_{max} (min)	480	20
AUC_{0-10} (mg h/mL)	1.04 ± 0.10	2.02 ± 0.07

the suspension, while, a burst release was sustained after 2 h, and overally, an enhanced release of curcumin from SNEDDS was observed.

Fig. 3 shows FESEM images of the curcumin loaded SNEDDS at different magnifications. The images reveal a spherical shape for the droplets in a range of 6–14 nm with an average size of 10 ± 4 nm in diameter. The results are in accordance with the finding obtained from particle size analyses.

For the quantitation of curcumin in rat plasma, a calibration curve for determination of curcumin was firstly constructed (Supplementary material S3) with a good linearity, a regression equation of $y = (19956 \pm 84)x + (73.6 \pm 38.8)$ and a correlation coefficient of 0.9999 over the concentration range of 0.004–1 mg/mL.

Time profiles of the mean concentrations of curcumin in plasma samples upon oral administration of curcumin loaded SNEDDS and the curcumin suspension at a dose of 100 mg/kg are presented in Fig. 4. The pharmacokinetic parameters of these formulations are presented in Table 3. After oral administration of curcumin suspension, the plasma level of curcumin was very low. On the other hand, the results showed that C_{max} of curcumin in the SNEDDS formulation was increased by 3.95 times, compared to the curcumin suspension. Mann-Whitney test revealed that there was a significant difference between the two groups for C_{max} ($p < 0.05$). In addition, T_{max} was shorter for SNEDDS; curcumin was absorbed rapidly and it reached its maximum concentration at a shorter time, when it was loaded in the SNEDDS. Finally, the oral bioavailability of curcumin loaded SNEDDS was enhanced by 194.2%, compared to curcumin suspension. The improved absorption of curcumin from SNEDDS can be arisen from its enhanced dissolution in the components, and releasing from an enhanced interfacial surface area [31] resulted from the very small droplets of the nanoemulsion. Alternatively, SNEDDS led to an enhanced lymphatic transport through transcellular pathway [38], and the content of surfactants in SNEDDS can help the permeability by disturbing the cell membrane [39].

4. Conclusion

A SNEDDS for curcumin was developed using simple, safe, easily available, and low-cost oil, surfactant and cosurfactant of ethyl oleate, tween 80, and PEG 600. The SNEDDS was characterized and its bioavailability was evaluated and compared with a curcumin suspension. It was found that SNEDDS caused an enhancement in C_{max}. Other formulations for SNEDDS with different amounts of the components can be considered for further evaluation of curcumin bioavailability. SNEDDS presented here may be expandable for increment in the bioavailability of other water poorly soluble drugs.

Conflict of interest

There is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.biopha.2017.01.102.

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