JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Article

pubs.acs.org/JAFC

Preparation and Enhancement of Oral Bioavailability of Curcumin Using Microemulsions Vehicle

Liandong Hu,*[,†] Yanhong Jia,[†] Feng Niu,[‡] Zheng Jia,[§] Xun Yang,[†] and Kuiliang Jiao[‡]

[†]College of Pharmacy, and Key Laboratory of Pharmaceutical Quality Control of Hebei Province, Hebei University, Baoding 071002, People's Republic of China

[‡]NBP Pharmaceutical Company Limited, CSPC Pharmaceutical Group Limited, Shijiazhuang 052165, People's Republic of China

[§]Department of Clinical Medecine, Tangshan Vocational and Technical College, Tangshan 063020, People's Republic of China

ABSTRACT: A new microemulsions system of curcumin (CUR-MEs) was successfully developed to improve the solubility and bioavailability of curcumin. Several formulations of the microemulsions system were prepared and evaluated using different ratios of oils, surfactants, and co-surfactants (S&CoS). The optimal formulation, which consists of Capryol 90 (oil), Cremophor RH40 (surfactant), and Transcutol P aqueous solution (co-surfactant), could enhance the solubility of curcumin up to 32.5 mg/mL. The pharmacokinetic study of microemulsions was performed in rats compared to the corresponding suspension. The stability of microemulsions after dilution was excellence. Microemulsions have significantly increased the C_{max} and area under the curve (AUC) in comparison to that in suspension ($p < 0.05$). The relative bioavailability of curcumin in microemulsions was 22.6-fold higher than that in suspension. The results indicated that the CUR-MEs could be used as an effective formulation for enhancing the oral bioavailability of curcumin.

KEYWORDS: *Curcumin, microemulsions, solubilization, oral bioavailability*

INTRODUCTION

Curcumin, a poorly water-soluble drug, is widely used in the food and chemical industry with coloring, flavoring, and preservative utility. Curcumin has several good biological activities and pharmacological actions, such as antitumor, anti-inflammatory, antivirus, antioxidation, and low toxicity, with promising clinical application.[1,2] Some studies reported that curcumin could induce apoptosis and suppress the formation of procarcinogens through various mechanisms in the last century.[3] Curcumin could also enhance oral absorption, oral bioavailability, and drug action of many drugs.[4,5] However, except for these benefits of curcumin, it also suffers from its extremely low water solubility, which is up to 11 ng/mL in plain aqueous buffer at pH 5.0,[6] and low oral bioavailability (only 1% in rats).[7,8] Curcumin, in addition, is unstable at neutral−basic pH values, which is degraded to vanillin, ferulic acid, and *trans*-6-(40-hydroxy-30-methoxy-phenyl)-2,4-dioxo-5-hexenal.[9] Recently, some approaches have been developed to improve the bioavailability of curcumin, such as loading curcumin into liposomes or nanoparticles, forming a curcumin−phospholipid complex, and synthesizing structural analogues of curcumin,[10,11] while preparing a self-microemulsion drug delivery system.[12]

Microemulsions are defined as a colloidal, optically isotropic, transparent, or slightly opalescent formulations, consisting of surfactant, co-surfactant (S&CoS), oil, and water.[13−15] Microemulsions have several advantages for pharmaceutical use, such as ease of preparation, long-term stability, and high drug solubilization capacity. Microemulsions are suitable for the incorporation of poorly water-soluble drugs to improve oral absorption.[16−21] In the field of functional foods, microemulsions have many applications in solving the problems of solubility as well as stability of nutraceuticals and food additives.

The main purpose of this study is to design, prepare, and characterize a microemulsions formulation of curcumin for oral administration. On the basis of a solubility study and pseudoternary phase diagrams, microemulsions of curcumin were developed after screening oils and S&CoS. The optimal formulation of curcumin was investigated by physicochemical characteristics, as well as the pharmacokinetic study in rats.

MATERIALS AND METHODS

Materials. Curcumin was obtained from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). Excipients, such as Labrafac Lipophile WL1349, Labrafil M 1944 CS, Capryol 90, Labrasol, and Transcutol P, were donated by Gattefosse (Shanghai, China). Cremophor RH40 was purchased from BASF Co., Ltd. (Germany). Tween 80, Span 80, ethanol, and propylene glycol were obtained from Meilin Industry and Trade Co., Ltd. (Tianjin, China). Ethyl oleate was purchased from Henan Kangyuan Spices Co., Ltd. (Zhengzhou, China). Isopropyl myristate (IPM) was obtained from Beijing Xinnuo Jiuheng Technology and Trade Co., Ltd. (Beijing, China). Peanut oil and soybean oil were purchased from Beijing Eisen-Lubao Co., Ltd. (Beijing, China). Acetonitrile and methanol were high-performance liquid chromatography (HPLC)-grade and supplied by Kermel Chemical (Tianjin, China). Double-distilled water was used throughout the study. All other chemicals and solvents were analytical-reagent-grade.

Preparation of Microemulsions. *Solubility Study.* To find out appropriate oils and surfactants in microemulsions, the solubility of curcumin in various mediums was investigated by adding excess curcumin into 2 mL of each medium (Table 1) in the centrifugal tube. Then, the centrifugal tubes containing the mixture were kept in a

Received: October 7, 2011
Revised: May 7, 2012
Accepted: May 14, 2012
Published: May 15, 2012

ACS Publications © 2012 American Chemical Society

Table 1. Solubility of Curcumin in Various Mediums (Mean ± SD; n = 3)

	medium	solubility of curcumin (mg/mL)
oil	peanut oil	0.17 ± 0.01
	Labrafac Lipophile WL1349	3.45 ± 0.11
	Labrafil M 1944CS	3.72 ± 0.13
	Capryol 90	9.89 ± 0.18
surfactant	Tween 80	2.18 ± 0.08
	Labrasol	8.42 ± 0.19
	Cremophor RH40	103.94 ± 14.12
	Span 80	2.50 ± 0.09
co-surfactant	Transcutol P	156.30 ± 21.71
	propylene glycol	6.52 ± 0.16
	ethanol	26.86 ± 0.62

shaking incubator at 20 °C for 2 days to obtain equilibrium. The equilibrated samples were filtered with the 0.45 μm Millipore filtration to remove the excess drug. After the appropriate dilution with methanol, the drug content was measured by HPLC mentioned below.

Construction of Pseudoternary Phase Diagrams. Pseudoternary phase diagrams were constructed to obtain the concentration range of components for the existing region of microemulsions. The weight ratio of oil/surfactant employed was 1:1, 1:2, and 1:3. Transcutol P aqueous solution (containing 10, 20, 30, 40, 50, 60, 70, 80, and 90% Transcutol P, v/v) was added dropwise to each mixture of oil and surfactant under gentle magnetic stirring at ambient temperature. The mixtures were assessed visually. The points from clarifying to turbid and turbid to clarifying were investigated. On the basis of these diagrams, appropriate Transcutol P aqueous solution was selected for the preparation of microemulsions system of curcumin (CUR-MEs).

Preparation of CUR-MEs. CUR-MEs were prepared at various component ratios according to the results of pseudoternary phase diagrams. Excess curcumin was dispersed to the mixture of oil and surfactant. Then, an appropriate amount of Transcutol P aqueous solution was added to the mixture drop by drop, and the mixture was stirred for 48 h at 25 °C under light shielding. The undissolved drug was removed by centrifugation, and the supernatant was filtered by a 0.45 μm membrane. After appropriate dilution with methanol, the concentration in the filtrate was measured by HPLC.

Physical Properties of Microemulsions. *Droplet Size of Microemulsions.* The droplet size and distribution of the CUR-MEs were measured by photon correlation spectroscopy (PCS) using a NICOMP particle sizing system (CW380, Santa Barbara, CA) at a fixed angle of 90°. The analysis data of droplet size were evaluated using volume distribution. All measurements were performed at 25 °C.

Transmission Electron Microscopy (TEM). The morphology of the microemulsions was observed by TEM (JEM-100SX, JEOL, Japan). One drop of diluted microemulsions samples was negatively stained by 2% phosphotungstic acid (PTA) and placed on copper grids followed by drying at room temperature before examination.

Viscosity. The viscosity of CUR-MEs and water were analyzed by a NDJ-1 rotational viscometer (Shanghai Anxuan Scientific Instrument Co., Ltd., Shanghai, China). All measurements were performed at 20 °C.

Stability of Microemulsions. CUR-MEs were diluted consecutively by 50, 100, and 200 times with distilled water. The drug-loading quantity of these diluted microemulsions was measured by HPLC. Then, the droplet size and appearance of these diluted microemulsions were investigated.

HPLC Analysis of Curcumin. All samples were analyzed by HPLC that consisted of a LC-20A liquid chromatogram and SPD-20A ultraviolet/visible (UV/vis) detector (Shimadzu, Kyoto, Japan) using a C18 column (5 μm, 250 × 4.6 mm, Bonna-Agela Technologies, Inc., Wilmington, DE) at room temperature. Curcumin was detected at 428 nm. The mobile phase was a mixture of methanol/H_2O (containing 3.6% glacial acetic acid) (70:30, v/v) at a flow rate of 1.0 mL/min.

***In Vivo* Absorption.** Healthy Sprague−Dawley rats were fasted for 12 h prior to experiments and supplied water only. They were randomized to be administered orally with curcumin suspension (1000 mg of curcumin/kg of body weight) or CUR-MEs alternatively (200 mg of curcumin/kg of body weight). Curcumin suspension [curcumin dispersed in 0.4% sodium carboxymethycellulose (CMC-Na) solution] was prepared. Blood samples were taken at 0, 30, 60, 120, 180, 240, 300, and 360 min after administration from the tail vein. Blood samples were collected in tubes containing heparin at various intervals after administration. Samples were centrifuged after collection and stored at −20 °C.

The plasma concentration of curcumin was determined by HPLC, which was previously reported (see the HPLC Analysis of Curcumin section). Briefly, 0.6 mL of ethanol was added to 0.2 mL of plasma and vortexed for 3 min. Finally, it was centrifuged at 1735*g* for 10 min, and the organic portion was separated and blown dry at 20 °C. The residues were reconstituted in 200 μL of methanol, and 20 μL was injected for analysis.

Statistical Analysis. All of the experiments in the study were performed at least 3 times, and the data were expressed as the mean ± standard deviation (SD). A two-tailed unpaired Student's t test was performed at $p < 0.05$.

RESULTS AND DISCUSSION

Solubility Study. The solubility of curcumin in various oils and S&CoS was analyzed to screen components for microemulsions. The results were shown in Table 1. Among the four test oils, curcumin showed the highest solubility in Capryol 90. Therefore, Capryol 90 was fixed as the oil phase for further studies.

Pseudoternary Phase Diagram Study. The pseudoternary phase diagram facilitated the determination of the components concentration range for the existence of microemulsions in the absence of curcumin. In this experiment, Cremophor RH40, Span 80, Labrasol, and Tween 80 as the surfactant were investigated with Capryol 90 as the oil phase. Propylene glycol, ethanol, and Transcutol P were used as the co-surfactant. Only Cremophor RH40 could form microemulsions. Therefore, it was used as the desirable surfactant.

Cremophor RH40 was used as the surfactant. Capryol 90 was used as the oil phase. Propylene glycol, ethanol, and Transcutol P were used as the co-surfactant. Three kinds of microemulsions were prepared by pairing the surfactants, oil phase, and three co-surfactants mentioned above. When these microemulsions were diluted 50 times with distilled water, only the one in which Transcutol P was used as the co-surfactant formed stable microemulsions dilution. Therefore, Transcutol P was chosen as the co-surfactant.

In addition, we performed an experiment about the addition method of co-surfactants. One was adding Transcutol P to the mixture of oil and surfactant, and the other was adding the Transcutol P aqueous solution to the mixture of oil and surfactant. When microemulsions were prepared by the first way, the primitive microemulsions were not stable and crystallized. Thus, the second way was adopted.

The phase diagrams, containing Cremophor RH40 as the surfactant, Capryol 90 as the oil phase, and Transcutol P, which was diluted with distilled water into the Transcutol P aqueous solution (containing 10, 20, 30, 40, 50, 60, 70, 80, and 90% Transcutol P, v/v), as the co-surfactant, were described in Figure 1. The translucent microemulsions region was presented in phase diagrams. No distinct conversion from water-in-oil (w/o) to oil-in-water (o/w) microemulsions was observed. The rest of the region on the phase diagram represented the turbid and conventional emulsions based on visual observation. The

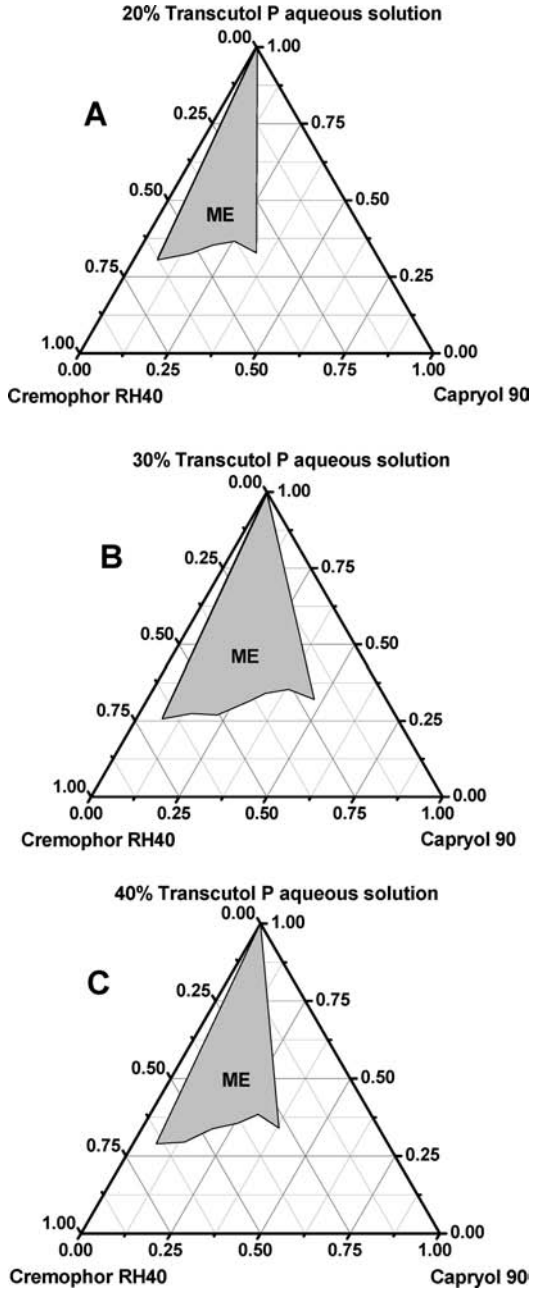

Figure 1. Pseudoternary phase diagrams of the oil–surfactant–co-surfactant aqueous solution system at (A) 20%, (B) 30%, and (C) 40% weight ratios of Transcutol P to the mixture of oil and surfactant at room temperature of 22 °C. The shaded areas represent the concentration range of components for the existing region of microemulsions.

Table 2. Compositions, Droplet Size, and Curcumin Content of the Selected Formulations (n = 3)

formulation	Capryol 90/Cremophor RH40/30% Transcutol P aqueous solution	droplet size (nm)	drug content (mg/mL)
F1	11:44:45	26.1 ± 1.1	10.3 ± 0.6
F2	14:44:42	27.3 ± 2.0	32.5 ± 1.5
F3	18:38:44	29.8 ± 2.2	38.2 ± 1.7

addition of Transcutol P increased more area of microemulsions at all volume rate values than that with Cremophor RH40 alone. It was also found that the microemulsions region was increased gradually with an increase in volume rate values, reaching a maximum at 30%. Thus, the volume rate of Transcutol P and water was fixed at 30% for further studies.

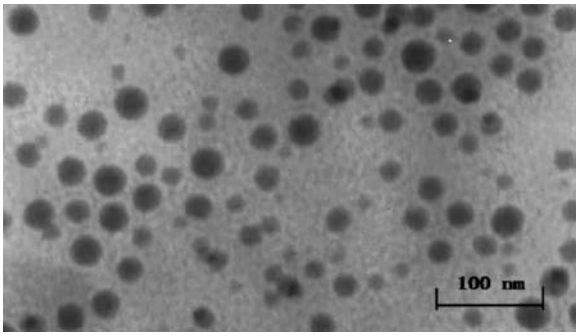

Figure 2. TEM of curcumin-loaded microemulsions.

Table 3. Compositions of the Selected Microemulsions Formulations and Droplet Size of the Formulation before and after Dilution (n = 3)

formulation	diluted times	droplet size (nm)
Capryol 90/Cremophor RH40/30% Transcutol P aqueous solution = 14:44:42	not diluted	27.3 ± 2.0
	50	27.7 ± 2.2
	100	27.8 ± 2.0
	200	27.8 ± 2.2

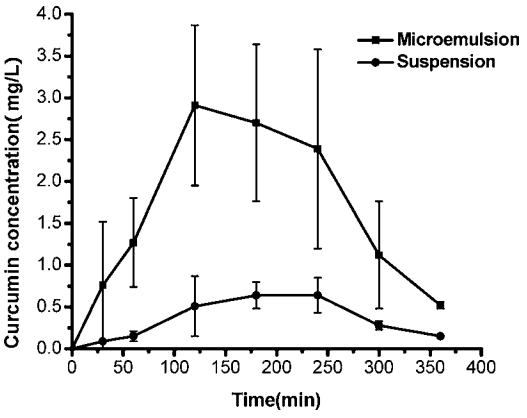

Figure 3. Blood concentration–time profile of curcumin after oral administration of suspension and microemulsions to rats: CUR-MEs (200 mg of curcumin/kg of body weight) and curcumin suspension (1000 mg of curcumin/kg of body weight) (mean ± SD; n = 6).

Table 4. Comparison of Pharmacokinetic Parameters between CUR-MEs (200 mg of Curcumin/kg of Body Weight) and Curcumin Suspension (1000 mg of Curcumin/kg of Body Weight) (Mean ± SD; n = 6)

group	microemulsion	suspension
$T_{1/2}$ (min)	63.06 ± 18.47	61.24 ± 15.17
C_{max} (mg/L)	3.57 ± 1.18	0.83 ± 0.83
T_{max} (min)	138.00 ± 78.23	180.00 ± 60.00
AUC (min mg L^{-1})	690.49 ± 150.05	153.21 ± 30.33
mean retention time (MRT) (min)	198.06 ± 7.03	217.59 ± 22.47

Solubility of Curcumin in Microemulsions. To find out optimized formulation with higher drug-loading capacity, curcumin was dissolved in the mixture of oil and surfactant

dx.doi.org/10.1021/jf204078t | J. Agric. Food Chem. 2012, 60, 7137–7141

Table 5. Comparison to Literature Data on the Absorption of Numerous Other Curcumin Compositions Developed To Enhance Curcumin Gastrointestinal Absorption

	our experimental group	our control group	literature cited 4	literature cited 8	literature cited 21	literature cited 27
experimental animals	Sprague–Dawley rats	Sprague–Dawley rats	Sprague–Dawley rats	rats	male Sprague–Dawley rats	male mice
administration dosage (mg of curcumin/kg of body weight)	200	1000	20	500	100	200
administration way	oral	oral	oral	oral	oral	oral
drug dosage form	CUR-MEs	curcumin suspension	curcumin nanoemulsion	powder	curcumin nanoparticles	self-microemulsifying drug delivery system
C_{max} (ng/mL)	3570 ± 1180	830 ± 830	451 ± 166	0.06 ± 0.01	260.5 ± 26.4	196.56
$T_{1/2}$ (min)	63.06 ± 18.47	61.24 ± 15.17	39 ± 10	44.5 ± 7.5		44.4
T_{max} (min)	138.00 ± 78.23	180.00 ± 60.00	8.7 ± 2.5	41.7 ± 5.4	120	30
AUC ($\mu g\ mL^{-1}\ min^{-1}$)	690.49 ± 150.05	153.21 ± 30.33	20.0 ± 6.4	3.6 ± 0.6	193.44 ± 20	166.56

and then miroemulsified by adding the Transcutol P aqueous solution. We had prepared many kinds of CUR-MEs according to the concentration of components for the existing region of microemulsions in the pseudoternary phase diagrams. The drug-loading capacity of the formulations F1, F2, and F3 was higher in comparison to others. Three kinds of microemulsions were formed by oil, co-surfactant, and 30% Transcutol P aqueous solution (w/w/w), whose ratio was selected from F1 (11:44:45), F2 (14:44:42), and F3 (18:38:44) separately for experiments. Among the three kinds of microemulsions, the solubility of curcumin was increased with the ratio of oil/surfactant (Table 2). F3 (38.2 mg/mL) produced a higher solubilizing capacity of curcumin than F1 (10.3 mg/mL) and F2 (32.5 mg/mL). Furthermore, the three kinds of microemulsions did not exhibit any precipitation of drug when they were observed for a period of 3 months. F3 solution, which was diluted 100 times with distilled water, was not stable, because curcumin began after 3 h. Therefore, the formulation consisting of 14% Capryol 90, 44 and 30% Cremophor RH40, and 42% Transcutol P aqueous solution (w/w) with high solubility of curcumin (32.5 mg/mL) was optimum CUR-MEs formulation.

Characterization of Microemulsions. The physicochemical characteristics of microemulsions appeared in Table 2. Morphology of the CUR-MEs was characterized using TEM (Figure 2). The average droplet size of microemulsions was around 27.3 nm (Table 2). Microemulsions were Newtonian fluids. Dynamic viscosity of microemulsions was 1.632 Pa s. All measurements were performed at 20 °C. Microemulsions were clear and transparent and turned light blue opalescent as they were substantially diluted with water. An experiment has been performed to measure the droplet size of microemulsions upon dilution (Table 3). A gradual increase with enhancing diluted times in droplet size of microemulsions was observed in our experiments. There might be the following reason: Microemulsions were diluted, which would lead to the concentration of the emulsifier to decrease in the microemulsions system, with the gradual reduction in the population of smaller liquid droplets made in aqueous phases. Coalescence took place between larger and smaller droplets.[22] In our study, no drugs crystallized out of the solution in 6 months after CUR-MEs were diluted consecutively by 50, 100, and 200 times with distilled water. The stability of microemulsions after dilution was good, which proved that CUR-MEs in excess water could avoid drug precipitation.

Pharmacokinetic Study. Figure 3 showed the average plasma concentration–time curve of curcumin after oral administration. The pharmacokinetic parameters were given in Table 4. The peak plasma concentration (C_{max}) and the time (T_{max}) were obtained directly from the individual plasma concentration versus time profiles. The pharmacokinetic data of Table 4 indicate that the C_{max} of CUR-MEs significantly increased ($p < 0.05$) compared to curcumin suspension. The area under the curve (AUC) of CUR-MEs was also significantly greater than that of curcumin suspension ($p < 0.05$). After oral administration of CUR-MEs, the relative bioavailability was 22.6-fold higher than that in curcumin suspension. It was concluded that the absorption of curcumin was enhanced significantly by employing the microemulsions formulation compared to curcumin suspension. Previous studies also show an enhanced oral bioavailability of some other drugs by employing the microemulsions formulation.[23−25]

The enhanced bioavailability was probably attributed to the following effects: First, solubility of curcumin was improved significantly. The solubility became 32.5 mg/mL by the optimum microemulsions, which was 2955 times as much as that (11 ng/mL) in plain aqueous buffer, and the liquid drug concentrations were proportional.[26,27] When the solubility of drug was improved, the permeation rate of CUR-MEs was significantly improved. No drug crystallized out of the solution; thus, CUR-MEs had a good stability after dilution. The gastrointestinal absorption could be increased by microemulsions, which could keep the drug as the soluble form. Thus, drug absorption was promoted.

Second, the high adhesion of microemulsions may make emulsion droplet closely contacted with the gastrointestinal tract in a long period; therefore, transmembrane transport of the drug in the gastrointestinal tract could be promoted. Curcumin suspension passed through the intestine rapidly by contrast. Meanwhile, there were many deudenum and jejunum villis; therefore, viscous microemulsions drops may be entrapmented easily. The stagnation time was extended. Microemulsions could be transported and increased by the M cell of intestina parietes lymphoid aggregate. Therefore, the absorption amount was augmented.

Extensive use of curcumin has been made in many fields; however, only when its solubility and bioavailability were fully increased, could the potential value of curcumin be developed. In this study, a new microemulsions system of curcumin for oral administration was constructed. Several formulations were evaluated to find an optimum microemulsions system that had high drug solubility. Finally, CUR-MEs composed of Capryol 90 (oil), Cremophor RH40 (surfactant), and Transcutol P aqueous solution (co-surfactant) could greatly enhance the solubility of curcumin up to 32.5 mg/mL. The oral

bioavailability of curcumin obtained from microemulsions was 22.6-fold higher than that in suspension.

Table 5 showed absorption of curcumin from CUR-MEs and compared it to literature data on the absorption of numerous other curcumin compositions developed to enhance curcumin gastrointestinal absorption. It was concluded that the absorption of curcumin was enhanced significantly by employing the microemulsions formulation compared to numerous other curcumin compositions. Furthermore, the ingredients above were all embodied, such as Capryol 90, NF; Cremophor RH40, USP/NF; and Transcutol P, EP/NF. Therefore, the safety of the ingredients was reliable. These findings suggested that CUR-MEs could be used as a potentially suitable dosage form in nutraceuticals and functional food area.

AUTHOR INFORMATION

Corresponding Author

*Telephone: +86-312-5971107. Fax: +86-312-5971107. E-mail: hbupharm@126.com.

Funding

This work was supported by the Talent Introduction Program of Hebei University (y2005064) and a grant by the Medical and Engineering Science Research Center of Hebei University (BM201109).

Notes

The authors declare no competing financial interest.

ABBREVIATIONS USED

CUR-MEs, microemulsions system of curcumin; S&CoS, surfactants and co-surfactants; AUC, area under the curve; HPLC, high-performance liquid chromatography; PCS, photon correlation spectroscopy; TEM, transmission electron microscopy; w/o, water-in-oil; o/w, oil-in-water; C_{max}, peak plasma concentration; T_{max}, peak plasma time; MRT, mean retention time

REFERENCES

(1) Araujo, C. C.; Leon, L. L. Biological activities of *Curcuma longa* L. *Mem. Inst. Oswaldo Cruz* **2001**, *96*, 723−728.

(2) Hsu, C. H.; Cheng, A. L. Clinical studies with curcumin. *Adv. Exp. Med. Biol.* **2007**, *595*, 471−480.

(3) Chauhan, D. P. Chemotherapeutic potential of curcumin for colorectal cancer. *Curr. Pharm. Des.* **2002**, *8* (19), 1695−1706.

(4) Onoue, S.; Takahashi, H.; Kawabata, Y.; Seto, Y.; Hatanaka, J.; Timmermann, B.; Yamada, S. Formulation design and photochemical studies on nanocrystal solid dispersion of curcumin with improved oral bioavailability. *J. Pharm. Sci.* **2010**, *4*, 1872−1880.

(5) Chueh, S. C. J.; Lai, M. K.; Liu, I. S.; Teng, F. C.; Chen, J. Curcumin enhances the immunosuppressive activity of cyclosporine in rat cardiac allografts and in mixed lymphocyte reactions. *Transplant. Proc.* **2003**, *35*, 1603−1605.

(6) Tonnesen, H. H.; Masson, M.; Loftsson, T. Studies of curcumin and curcuminoids. XXVII. Cyclodextrin complexation: Solubility, chemical and photochemical stability. *Int. J. Pharm.* **2002**, *244*, 127−135.

(7) Pan, M. H.; Huang, T. M.; Lin, J. K. Biotransformation of curcumin through reduction and glucuronidation in mice. *Drug Metab. Dispos.* **1999**, *27*, 486−494.

(8) Yang, K. Y.; Lin, L. C.; Tseng, T. Y.; Wang, S. C.; Tsai, T. H. Oral bioavailability of curcumin in rat and the herbal analysis from *Curcuma longa* by LC−MS/MS. *J. Chromatogr., B: Anal. Technol. Biomed. Life Sci.* **2007**, *853*, 183−189.

(9) Huang, M. T.; Lou, Y. R.; Ma, W.; Newmark, H. L.; Reuhl, K. R.; Conney, A. H. Inhibitory effects of dietary curcumin on forestomach duodenal and colon carcinogenesis in mice. *Cancer Res.* **1994**, *54* (22), 5841−5847.

(10) Marczylo, T. H.; Verschoyle, R. D.; Cooke, D. N.; Morazzoni, P.; Steward, W. P.; Gescher, A. J. Comparison of systemic availability of curcumin with that of curcumin formulated with phosphatidylcholine. *Cancer Chemother. Pharmacol.* **2007**, *60*, 171−177.

(11) Anand, P.; Kunnumakkara, A. B.; Newman, R. A.; Aggarwal, B. B. Bioavailability of curcumin: Problems and promises. *Mol. Pharmacol.* **2007**, *4*, 807−818.

(12) Cui, J.; Yu, B.; Zhao, Y.; Zhu, W. W.; Li, H. L.; Lou, H. X.; Zhai, G. X. Enhancement of oral absorption of curcumin by self-microemulsifying drug delivery systems. *Int. J. Pharm.* **2009**, *371*, 148−155.

(13) Kreuter, J. *Colloidal Drug Delivery Systems*; CRC Press (Taylor and Francis Group): Boca Raton, FL, 2009.

(14) Chen, H. B.; Chang, X. L.; Du, D. R.; Li, J.; Xu, H. B.; Yang, X. L. Microemulsion-based hydrogel formulation of ibuprofen for topical delivery. *Int. J. Pharm.* **2006**, *315*, 52−58.

(15) Tenjarla, S. Microemulsions: An overview and pharmaceutical applications. *Crit. Rev. Ther. Drug Carrier Syst.* **1999**, *16*, 461−521.

(16) Lawrence, M. J.; Rees, G. D. Microemulsion-based media as novel drug delivery systems. *Adv. Drug Delivery Rev.* **2000**, *45*, 89−121.

(17) Gasco, M. R. Microemulsions in the pharmaceutical field: Perspectives and applications. *Industrial Applications of Microemulsions*; Marcel Dekker, Inc.: New York, 1997.

(18) Kim, C. K.; Ryuu, S. A.; Park, K. M.; Lim, S. L.; Hwang, S. J. Preparation and physiochemical characterization of phase inverted water/oil microemulsion containing cyclosporin A. *Int. J. Pharm.* **1996**, *147*, 131−134.

(19) Gao, Z.-G.; Choi, H.-G.; Shin, H.-J.; Park, K.-M.; Lim, S.-J.; Hwang, K.-J.; Kim, C.-K. Physicochemical characterization and evaluation of a microemulsion system for oral delivery of cyclosporin A. *Int. J. Pharm.* **1998**, *161*, 75−86.

(20) Ganta, S.; Devalapally, H. K.; Amiji, M. Curcumin enhances oral bioavailability and anti-tumor therapeutic efficacy of paclitaxel upon administration in nanoemulsion formulation. *J. Pharm. Sci.* **2010**, *11*, 4630−4641.

(21) Shaikh, J.; Ankola, D. D.; Beniwa, V.; Singh, D.; Ravi Kumarb, M. N. V. Nanoparticle encapsulation improves oral bioavailability of curcumin by at least 9-fold when compared to curcumin administered with piperine as absorption enhancer. *Eur. J. Pharm. Sci.* **2009**, *37*, 223−230.

(22) Wang, X. P.; Li, Z. Q.; Qiang, Y. Y.; Xiong, Y. J.; Wu, X. H.; Yu, J. Y.; Cao, G. Y.; Jiang, B. N. An investigation of coalescence of emulsified droplets in system crude oil/ASP flooding solution. *Oilfield Chem.* **1999**, *16*, 353−355.

(23) Yin, Y. M.; Cui, F. D.; Mu, C. F.; Choi, M. K.; Kim, J. S.; Chung, S. J.; Shim, C. K.; Kim, D. D. Docetaxel microemulsion for enhanced oral bioavailability: Preparation and in vitro and in vivo evaluation. *J. Controlled Release* **2009**, *140*, 86−94.

(24) Zhang, Q. Z.; Jiang, X. G.; Jiang, W. M.; Lu, W.; Su, L. N.; Shi, Z. Q. Preparation of nimodipine-loaded microemulsion for intranasal delivery and evaluation on the targeting efficiency to the brain. *Int. J. Pharm.* **2004**, *275*, 85−96.

(25) Park, K. M.; Kim, C. K. Preparation and evaluation of flurbiprofen-loaded microemulsion for parenteral delivery. *Int. J. Pharm.* **1999**, *181*, 173−179.

(26) Zhang, Z. Q.; Lu, B. Research overview of microemulsion-based media as novel drug delivery systems. *Adv. Drug Delivery Rev.* **2001**, *45*, 89−121.

(27) Wu, X.; Xu, J. H.; Huang, X. W.; Wen, C. X. Self-microemulsifying drug delivery system improves curcumin dissolution and bioavailability. *Drug Dev. Ind. Pharm.* **2011**, *37* (1), 15−23.