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Improving the Oral Bioavailability of Curcumin Using Novel Organogel-Based Nanoemulsions

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ABSTRACT: Curcumin is a natural bioactive compound with many health-promoting benefits. Its low oral bioavailability limits its application in functional foods. In the present study, novel organogel-based nanoemulsions have been developed for oral delivery of curcumin and improvement of its bioavailability. Recently developed curcumin organogel was used as the oil phase in the curcumin nanoemulsion formulation. Tween 20 was selected as the emulsifier on the basis of maximum in vitro bioaccessibility of curcumin in the nanoemulsion. In vitro lipolysis profile revealed that the digestion of nanoemulsion was significantly faster and more complete than the organogel. Permeation experiments on Caco-2 cell monolayers suggested that digestion-diffusion was the major absorption mechanism for curcumin in the nanoemulsion. Furthermore, in vivo pharmacokinetics analysis on mice confirmed that the oral bioavailability of curcumin in the nanoemulsion was increased by 9-fold compared with unformulated curcumin. This novel formulation approach may also be used for oral delivery of other poorly soluble nutraceuticals with high loading capacity, which has significant impact in functional foods, dietary supplements and pharmaceutical industries.

KEYWORDS: *bioavailability, curcumin, lipolysis, nanoemulsion, organogel*

INTRODUCTION

Curcumin is the major curcuminoid compound found in the rhizome of plant turmeric (*Curcuma longa*), along with demethoxycurcumin (D-Cur) and bisdemethoxycurcumin (BD-Cur). It is found that curcumin has multiple health-promoting properties, such as anticancer, anti-inflammatory, and antioxidant activities,[1−3] as confirmed in several clinical studies.[4−6] Meanwhile, it is also demonstrated that curcumin shows no toxicity in human at several grams per day for months.[5,7]

However, curcumin bears low oral bioavailability.[8] Multiple studies examined the pharmacokinetics profile of curcumin from oral administration in human and rodents. The highest plasma concentrations reported are 0.051 μg/mL from 12 g curcumin in human,[9] 1.35 ± 0.23 μg/mL from 2 g/kg in rat, and 0.22 μg/mL from 1 g/kg in mouse.[10]

Solubilization, permeation, and metabolism are three important factors affecting the oral bioavailability. In the case of curcumin, the water solubility is estimated as only 11 ng/mL, and most of the orally administered curcumin is usually found in feces.[11] The permeation mechanism of solubilized curcumin is passive diffusion and the rate is fairly high.[12,13] Curcumin is found to undergo rapid metabolism after/alongside permeation. The major metabolites from oral administration are curcumin sulfate and curcumin glucuronide.[10,14]

In the scope of food science, solubilization is usually the major target to improve the oral bioavailability of curcumin. Among different types of delivery systems, lipid-based formulations are able to generate mixed micelles after digestion, which are able to solubilize curcumin in the aqueous solution in the small intestine lumen.[15] Multiple lipid-based formulations including regular oil-in-water (O/W) emulsions,[16,17] self-microemulsifying systems,[18] microemulsions[19,20] and solid lipid nanoparticles have been developed for oral delivery of curcumin.[21−25] Studies have shown that curcumin has better oral bioavailability or in vivo bioactivity when it was encapsulated in emulsions.[16,18,25]

Recently, we developed a novel organogel for curcumin encapsulation and oral delivery. In vitro digestion of the organogel leads to high percentage of curcumin bioaccessibility. Meanwhile, the loading of curcumin in the organogel is high (2.6% total curcuminoids, 2.1% curcumin), achieved by using Span 20 to increase the solubility of curcumin in the oil and monostearin as the organogelator to stabilize curcumin from crystallization.[26]

Direct oral administration of the organogel may be inconvenient and emulsification of the organogel may provide additional benefits and increase the application versatility. Meanwhile, the in vivo oral bioavailability of curcumin in the organogel is yet to be examined. Therefore, to continue our study, this work focused on development of organogel-based O/W nanoemulsion. The emulsifier was selected to achieve maximum in vitro bioaccessibility. The in vivo fate of the nanoemulsion after oral administration was examined using in vitro lipolysis assay and Caco-2 cell monolayers permeation assay. The oral bioavailability was then investigated using experimental animals. The present work may provide more convenient solution for oral delivery of curcumin organogel and also shed light on the absorption mechanism of food nanoemulsions.

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MATERIALS AND METHODS

Materials. Curcumin (82% curcumin, 15% D-Cur and 3% BD-Cur) was provided by Sabinsa Corporation. Medium chain triacylglycerols (MCT, Neobee 1053) were obtained from the Stepan Company. Modified starch (HiCap 100) was obtained from National Starch. Whey protein isolate (WPI) was from Davisco Foods International, and 1-monostearin (about 60% purity) was from TCI America. Lecithin (Phospholipon 85G) was provided by Lipoid. Pancreatin with 8X USP specification (P7545), sulfatase (S9626), and glucuronidase (G7017) were obtained from Sigma Aldrich. Additionally, analytical grade β-17-estradiol acetate, Tween 20 [Polyoxyethylene (20) sorbitan monolaurate], Span20 (sorbitan monolaurate), and Tris maleate, sodium taurodeoxycholate (Na TDC) and glacial acetic acid and HPLC-grade acetonitrile and H_2O were used in this study.

All of the cell culture media and reagents were purchased from Fisher Scientific. Transwell permeable polycarbonate inserts (0.4 μm) and 12-well cell culture plates were obtained from Corning.

Preparation of Curcumin Organogel and Organogel-Based Nanoemulsions. Curcumin organogel was prepared as previously described,[26] with increased curcumin loading. Briefly, Span 20-saturated MCT, monostearin, and curcumin were mixed at the ratio of 10:2:1.2 (w/w/w, about 9% curcumin in organogel), followed by heating to dissolve curcumin completely and then setting at ambient temperature.

To prepare curcumin organogel-based nanoemulsions, water, organogel and emulsifier (modified starch, WPI, or Tween 20) were mixed at the weight ratio of 3:2:1 for about 5 min at about 100 rpm using a mechanical stirrer with a pitched blade impeller and then ultrasonicated using a tip sonicator at about 175 W for accumulatively 5 min.

Particle Size Measurement. Nanoemulsions were diluted 200 times into deionized water (dH_2O) and mixed well. The average particle sizes (hydrodynamic diameters) of the lipid droplets were determined with dynamic light scattering method using a BIC 90Plus particle size analyzer (Brookhaven Instrument, NY) at a fixed scattering angle of 90° at ambient temperature, with a solid-state laser operating at 658 nm with 30 mW power.[27] The scattering signals were detected by a high-sensitivity avalanche photodiode detector.

In Vitro Lipolysis of Formulations. In vitro lipolysis was performed according to our previous work.[26] Briefly, 0.25 g organogels or 0.75 g nanoemulsions were digested using pancreatin under fast state for 30 min at 37 °C. The pH of the solution was maintained at 7.5 by adding NaOH manually. The amount of NaOH added over time was recorded throughout the digestion. After digestion, the mixture was ultracentrifuged and the amount of curcumin in the aqueous phase was determined using HPLC.

The extent of lipolysis in this pH-stat titration was determined using the consumed NaOH amount.

$$\text{extent}_{\text{lipolysis}} = \frac{\text{NaOH amount consumed}}{\text{theoretical NaOH amount for complete lipolysis}} \times 100\% \quad (1)$$

To calculate the amount of NaOH required for complete lipolysis, it was assumed that digestion of 1 molecule of MCT, monostrearin, and Tween 20 consumed 2, 1, and 1 molecule of NaOH, respectively.

From the HPLC quantification, the percent bioaccessibility of curcumin was calculated as follows:

$$\%\text{bioaccessibility} = \frac{\text{amount of solubilized curcuminoids in aqueous phase}}{\text{amount of curcuminoids in the formulations}} \times 100\% \quad (2)$$

Determination of the Permeation Rate Across Caco-2 Cell Monolayers. The procedures for Caco-2 cell monolayers permeation assay followed our previous study.[12] Briefly, Caco-2 cell (passage number 35–45) monolayers were used after 21–29 days of culture, and 20 μg/mL free curcumin (by DMSO dispersion) or formulated curcumin was added into the apical compartment (HBSS + 10 mM methanesulfonic acid, pH 6.5). After different time intervals (15, 30, 45, and 60 min), media in the basolateral compartment (HBSS + 25 mM HEPES + 4% BSA, pH7.4) were removed and two volumes of acetonitrile were added before the HPLC analysis of curcumin. The apparent permeation rate was calculated as follows:

$$P_{\text{app}} = \left(\frac{dQ}{dt}\right)\left(\frac{1}{AC_0}\right) \quad (3)$$

where P_{app} is the apparent permeation rate, dQ/dt is the mass transport rate, A is the surface area of the insert; and C_0 is the initial curcumin concentration in the apical compartment (20 μg/mL).

For digested curcumin nanoemulsion, the mixed micelle aqueous solution obtained from the lipolysis was first heated at 95 °C for 5 min to inactivate enzymes, such as protease in the pancreatin, before the permeation assay.

High Performance Liquid Chromatography (HPLC) Analysis. HPLC quantification of curcumin was performed using an UltiMate 3000 HPLC system with a 25D UV–vis absorption detector (Dionex) and a Nova-Pak C18 3.9 × 150 mm column (Waters). Mobile phase solvents were: (A) water with 2% acetic acid, and (B) acetonitrile. Elution condition was as follows: 0 to 2 min, 65% A and 35% B; 2 to 17 min, linear gradient from 65% A and 35% B to 45% A and 55% B; 17 to 22 min, held at 45% A and 55% B; 22 to 23 min, mobile phase went back to 65% A and 35% B. Flow rate was 1 mL/min. Fifty microliters of samples were injected. Detection wavelength was set at 420 nm for curcuminoids and 280 nm for β-17-estradiol acetate in the pharmacokinetics studies.

Pharmacokinetics Analysis on Mice. Female CD-1 mice (22–26 g) were used in the pharmacokinetics analysis of curcumin (Rutgers University protocol no.: 99–015). After fast overnight, mice were administrated with curcumin nanoemulsion or curcumin water suspension at the dose of 240 mg/kg by oral gavage. At different time intervals (0.5, 1, 2, 4, 8, 12, and 24 h), blood samples were withdrawn by cardiac puncture. After centrifugation at 5000 ×g for 15 min at ambient temperature, plasma was removed and stored at −80 °C until HPLC analysis.

Before HPLC quantification, 150 μL plasma samples were incubated with equal volume of enzyme solutions (10 mg/mL sulfatase and 10 μL/mL of glucuronidase in 0.1 M sodium acetate buffer, pH 5.0) at 37 °C for 1 h to convert curcumin sulfate and glucuronide to free curcumin. Subsequently, 10 μL 1 mg/mL β-17-estradiol acetate in ethyl acetate was added as the internal control.[28] After extracted with ethyl acetate for three times and redissolved in 1:2 (v/v) dH_2O: acetonitrile, the samples were ready for HPLC analysis.

The areas-under-the curve (AUC) for the plot of the plasma concentration over time were calculated using linear trapezoidal method. $C_{\max}$ and $T_{\max}$ were directly obtained from the curves. K_{el} was estimated using the method of residuals, based on oral absorption one-compartment model.

Statistical Analysis. Student t test, Pearson Product Moment Correlation and One-way Analysis of Variance (ANOVA) were performed using SigmaPlot 10.0 software with SigmaStat integration (Systat Software).

RESULTS

In our previous work, food-grade organogel was developed for curcumin oral delivery with high in vitro bioaccessibility and curcumin loading.[26] In the present study, curcumin organogel containing 9% curcumin was used as the oil phase to prepare curcumin nanoemulsion. The absorption mechanism of curcumin nanoemulsion was examined and the oral bioavailability of curcumin in the nanoemulsion was investigated.

Choice of the Emulsifier for the Preparation of Organogel-Based Nanoemulsion. To develop curcumin organogel-based nanoemulsions, three common emulsifiers, modified starch, WPI and Tween 20, were compared in terms

of the in vitro bioaccessibility of curcumin after lipolysis. As shown in Figure 1A, the in vitro bioaccessibility of curcumin for

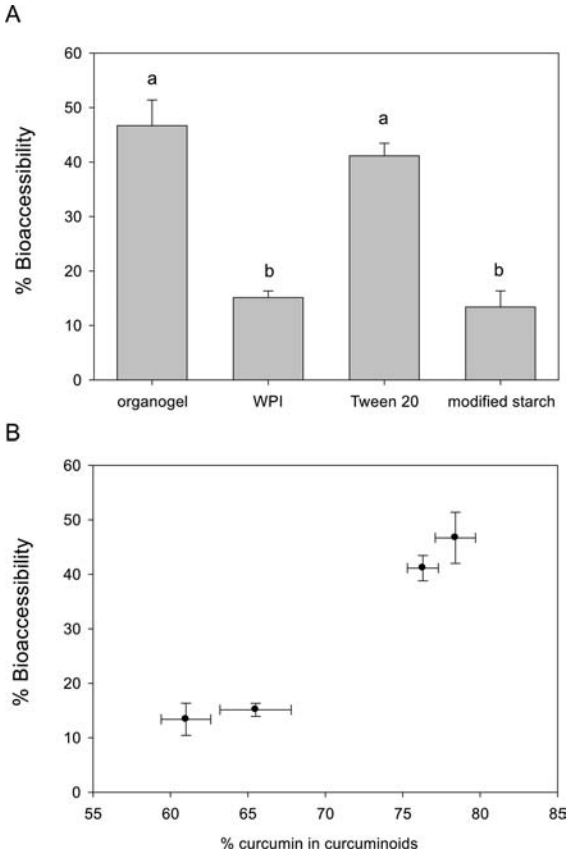

Figure 1. Selection of the emulsifier based on the percent bioaccessibility after in vitro lipolysis. (A) Comparison of the percent bioaccessibility of curcumin from different organogel-based nanoemulsions and the organogel. Different letters indicate significant difference. (B) Correlation of the percent bioaccessibility with the percentage of curcumin in the total solubilized curcuminoids. Data are presented as mean ± standard deviation (n = 3).

organogel and organogel-based emulsions ranged from 13% to 47%. From One-way ANOVA analysis, it was revealed that Tween 20 emulsion was able to generate similar in vitro bioaccessibility as the organogel, while modified starch- and WPI-emulsified emulsions showed significantly lower bioaccessibility. Therefore, Tween 20 was selected as the emulsifier to generate organogel-based emulsions.

The observation in Figure 1A also suggests that the structure of organogel was generally maintained after homogenization. Without monostearin, Span 20 saturated MCT was able to solubilize high amount of curcumin.[26] However, after emulsification, significant precipitation of curcumin was noticed and the bioaccessibility of curcumin was greatly decreased (unpublished results). In comparison, the lipolysis assays in Figure 1A demonstrated that bioaccessibility of curcumin in the nanoemulsion was similar to the original organogel, and little curcumin precipitation was noticed after centrifugation.

Since the curcumin raw material used in this study contained D-cur and BD-cur, the percentage of each of these three curcuminoids in the aqueous solution obtained from the lipolysis was also determined (Table 1). In the raw material, curcumin accounted for 82% of total curcuminoids, which was higher than that in all the digested formulations. Following the

Table 1. Percentage of Each Curcuminoid Component in the Raw Material and Solubilized Fraction after Lipolysis of Formulations[a]

	curcumin (%)	D-cur (%)	BD-cur (%)
raw material[A]	82.1 ± 1.0	14.8 ± 0.5	3.1 ± 0.5
organogel[B]	78.4 ± 1.3	16.4 ± 1.0	5.1 ± 0.4
WPI emulsion[C]	65.5 ± 2.3	24.3 ± 1.1	10.2 ± 1.2
Tween 20 emulsion[B]	76.3 ± 1.0	18.0 ± 0.7	5.7 ± 0.3
modified starch emulsion[C]	61.0 ± 1.6	27.0 ± 1.1	12.0 ± 0.5

[a]Different letters indicate significant difference in the percentage of curcumin. Data are presented as mean ± standard deviation (n = 3, except for raw material, n = 12).

same trend as the in vitro bioaccessibility (Figure 1A), the percentage of curcumin for organogel was similar to that for the Tween 20 emulsions, but higher than WPI and modified starch emulsions (One-way ANOVA). It was also noticeable that the in vitro bioaccessibility correlated positively with the percentage of curcumin in the three curcuminoids (Figure 1B, Pearson Product Moment Correlation, correlation coefficient 0.984, P Value 0.0164). Higher percentage of curcumin in the solubilized curcuminoinds after lipolysis corresponded to higher in vitro bioaccessibility of curcumin. Previously, it was demonstrated that at weak alkaline conditions, D-cur and BD-cur degraded more slowly than curcumin, leading to decreased curcumin percentage over time.[27] Considering that the in vitro lipolysis was performed at pH 7.5, it was suggested that different emulsifiers had different protection effect on curcumin during lipolysis, which resulted in different curcumin bioaccessibility and curcumin percentage. It was also noticed that the in vitro bioaccessibility of curcuminoids in organogel was lower than what was reported previously.[26] The reason may lie in that the curcumin loading in the organogel was increased significantly from about 2.6% to 9%.

Since Tween 20 was selected as the emulsifier for organogel-based nanoemulsions, the particle size of the organogel particles after emulsification was determined using dynamic light scattering (Figure 2). It was shown that the average diameter was 218 nm. The polydispersity was 0.280, suggesting a narrow distribution.

Comparison of the in Vitro Lipolysis Profile between Organogel and Organogel-Based Nanoemulsion. In the process to determine the in vitro bioaccessibility, the lipolysis titration profile (the extent of lipolysis over time) was also recorded. Although Tween 20 nanoemulsion and organogel

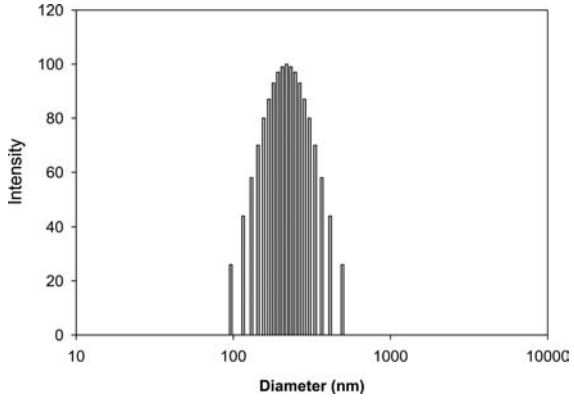

Figure 2. Particle size distribution of Tween-20 nanoemulsion.

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were able to generate similar in vitro bioaccessibility, their lipolysis titration profiles were distinct. As shown in Figure 3A,

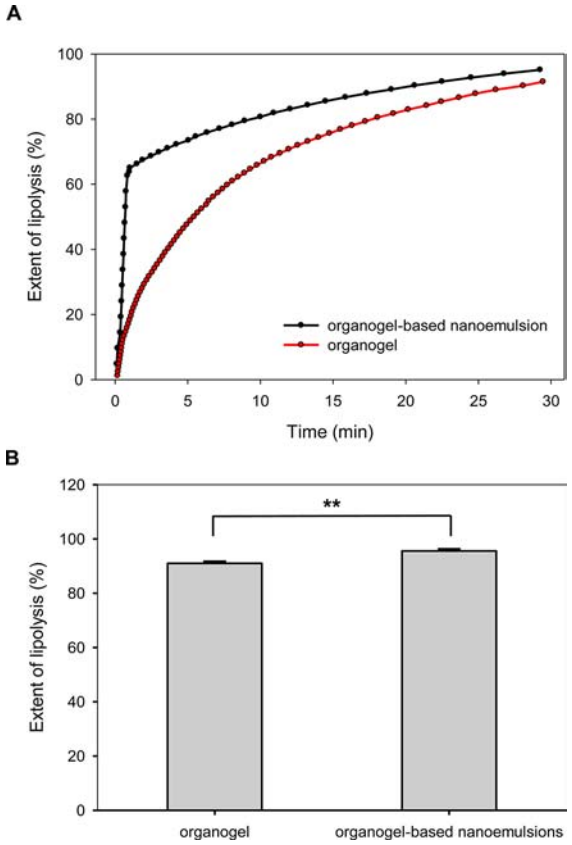

Figure 3. Comparison of the in vitro lipolysis of the organogel and organogel-based Tween 20 nanoemulsion, in the aspect of (A) the lipolysis profile and (B) the extent of lipolysis. Data in (B) are presented as mean ± standard deviation (n = 3). ** indicates that the difference is significant (p < 0.01)

the initial digestion rate for nanoemulsion was much higher than the organogel. The reason may lie in the difference in the surface area of the lipid particles. With smaller droplet size, nanoemulsions had much larger surface area for lipase-catalyzed lipid hydrolysis.[29] Meanwhile, after 30 min digestion, the extent of lipolysis for organogel-based nanoemulsion was also significantly greater than the organogel (Figure 3B), suggesting that digestion of nanoemulsions was more complete.

Examination of the Permeation Mechanism of Curcumin in the Nanoemulsion. The permeation mechanism for curcumin in the organogel-based nanoemulsion was investigated using Caco-2 cell monolayers to mimic the small intestine epithelium. There are two possible mechanisms for curcumin nanoemulsion permeation: (1) Nanoemulsions would be digested by lipase and simultaneously curcumin is solubilized by bile salts-fatty acids mixed micelles. Subsequently, solubilized curcumin passively diffuses across the epithelium layer.[12,13] This represents the classic digestion–diffusion route applicable for all the regular lipid-based formulations; (2) intact nanoemulsions, because of their small size, would be able to directly diffuse across the small intestine layer without digestion.[30]

To illustrate the permeation mechanism of curcumin in the organogel-based nanoemulsion, permeation experiments across Caco-2 cell monolayers were performed. The curcumin permeation rates for unformulated curcumin (by DMSO dispersion), intact nanoemulsion and digested nanoemulsion were compared (Figure 4A). It was shown from One-way

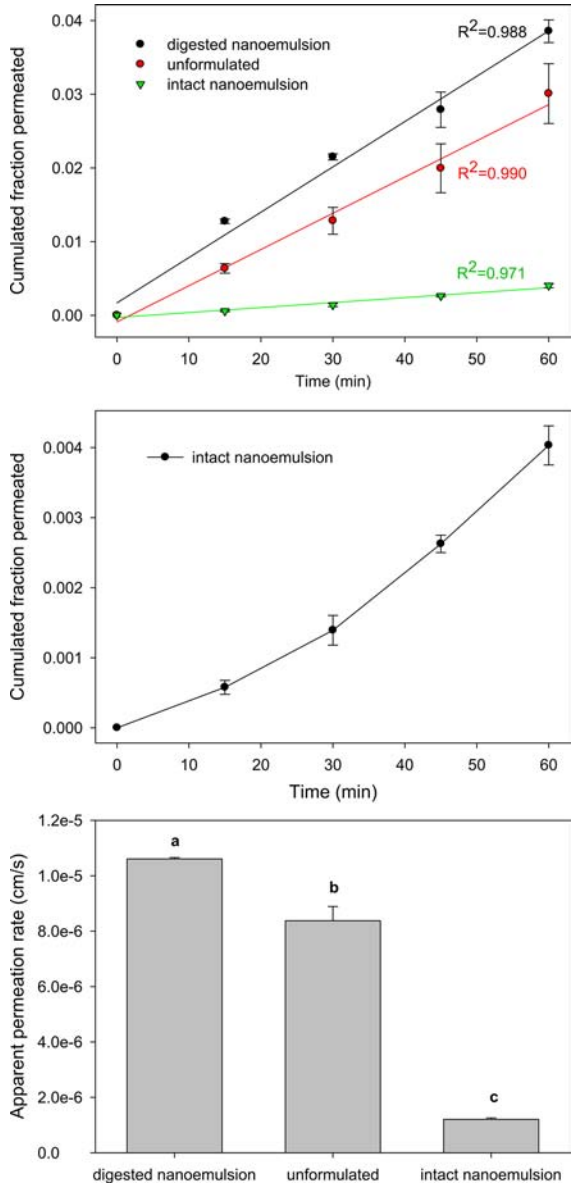

Figure 4. Determination of the curcumin permeation rates in unformulated form, intact nanoemulsion and digested nanoemulsion. (A) The cumulative fractions of curcumin transported from the three formulations. (B) The cumulative fraction of curcumin transported from the intact nanoemulsion only, showing the increasing permeation rate. (C) Comparison of the permeation rates of curcumin from the three formulations. Data are presented as mean ± standard deviation (n = 3).

ANOVA that curcumin from the digested nanoemulsion had the highest permeation rate, followed by unformulated curcumin. In contrast, curcumin in the intact nanoemulsions permeated the most slowly. Although these results alone could not exclude the possibility that intact nanoemulsions were able to permeate directly across the Caco-2 cell monolayers, it still suggested that the major permeation mechanism for curcumin nanoemulsion was the digestion-diffusion route. Furthermore, by closely looking at the permeation curve for curcumin from

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the intact nanoemulsion, one notes that the slope of the curve increased as a function of time (Figure 4B) and the transepithelial electric resistance (TEER) value did not change significantly (not shown), suggesting that the available curcumin in the donor compartment increased over time, which may result from the release of curcumin from the lipid phase of the nanoemulsion to the aqueous phase. This result further confirmed that digestion-diffusion was the major permeation mechanism for curcumin nanoemulsions. Before its absorption, curcumin may need to be solubilized in the aqueous phase, either by digestion of the lipid phase or diffusion from the nanoemulsion.

The permeation rate for unformulated curcumin was determined as $8.4 \pm 0.5 \times 10^{-6}$ cm/s in this study, which was similar to what we reported previously [$7.1 \pm 0.7 \times 10^{-6}$ cm/s,[12] Student's t test, $p > 0.05$].

Evaluation of the Oral Bioavailability of Curcumin in the Nanoemulsion. To directly investigate the oral bioavailability of curcumin in the organogel-based nanoemulsion, pharmacokinetics analysis was performed on mice after oral administration with curcumin water suspension or curcumin nanoemulsions. Since no curcumin was detected above the limit of detection from the plasma of the mice treated with unformulated curcumin, all of the plasma samples were incubated with glucuronidase and sulfatase to convert curcumin glucuronide and sulfate, the major curcumin metabolites from oral administration, back to curcumin before the HPLC quantification. As shown in Figure 5A–C, the plasma concentrations of total curcuminoids, curcumin and D-cur of the nanoemulsion were all apparently higher than those of unformulated curcumin. The pharmacokinetics parameters are listed in Table 2. Notably, the C_{max} of total curcuminoids, curcumin and D-cur increased by 18.4, 18.7, and 14.8 folds, respectively, and the $AUC_{0-\infty}$ increased by 9.3, 9.8, and 8.5 folds, respectively, demonstrating that the nanoemulsion formulation was able to improve the oral bioavailability (BA) of curcumin(oids).

The elimination rates (K_{el}) of curcumin and D-Cur were also obtained from the pharmacokinetics analysis. In both types of formulations, K_{el} of D-Cur was about 36% higher than that of curcumin (Table 2). To the best of our knowledge, it is the first time that the difference in the elimination rates between different curcuminoids has been discovered.

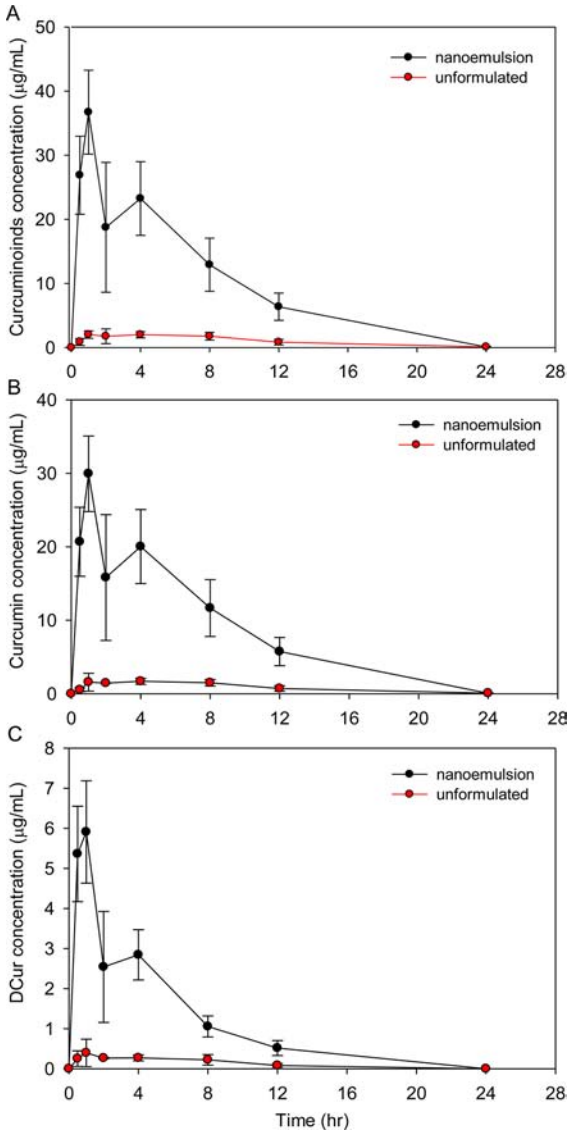

Figure 5. Plasma concentrations of (A) total curcuminoids, (B) curcumin, and (C) D-cur after enzyme treatment, from unformulated curcumin and curcumin nanoemulsion. Data are presented as mean ± standard error of the mean (n = 3 or 4).

DISCUSSION

In this work, organogel-based nanoemulsions were developed for encapsulation and oral delivery of curcumin. Tween 20 was selected as the emulsifier based on the in vitro bioaccessibility from lipolysis experiments. Using Caco-2 cell monolayers model, it was suggested that digestion–diffusion may be the major permeation mechanism for curcumin. Meanwhile, in vivo pharmacokinetic analysis confirmed that the oral bioavailability of curcumin in the nanoemulsion increased significantly compared to unformulated curcumin.

Solubilization and metabolism are two main hurdles for the oral bioavailability of curcumin. The organogel-based formulation developed here targeted the solubilization since the selection of formulation composition was based on in vitro bioaccessibility of curcumin after mimicked digestion (in vitro lipolysis assay). The effect of formulations on curcumin metabolism needs to be addressed by comparing the ratio of curcumin to its metabolites between oral administration of formulated and unformulated curcumin. However, the plasma concentration of curcumin from unformulated treatment was too low to be detected and therefore, no conclusions were drawn on the effect of formulation on the curcumin metabolism.

However, it is not expected that the formulation would affect the curcumin metabolism, especially the first-pass hepatic metabolism. In some scenarios, lipid-based formulation would enable the encapsulated highly lipophilic (c log $P > 5$) compounds to escape the first-pass metabolism.[15] Since the c log P value of curcumin is only 3.2 (PubChem, CID969516) and the lipid phase does not consist of long-chain triglycerides, it is not anticipated that curcumin delivered using the nanoemulsion will be incorporated in chylomicrons and escape the first-pass metabolism.[15] Therefore, the increased oral bioavailability from formulation may largely be attributed to the increase in the solubilization.

The permeation mechanism of the nanoemulsion was examined using in vitro Caco-2 cell monolayer model. It was demonstrated that the permeation rate of curcumin was

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Table 2. Pharmacokinetics Parameters of Curcumin Formulations after Oral Administration[a]

formulation	compounds	dose (mg/kg)	C_{max} (μg/mL)	T_{max} (h)	K_{el} (h^{-1})	$AUC_{0\text{-}inf}$ (μg/mL·min)	relative BA
water dispersion (unformulated)	total curcuminoids	240	2.0 ± 1.1	1	0.108	26.1	
	curcumin	197	1.6 ± 1.2	1	0.108	21.4	
	D-cur	36	0.4 ± 0.3	1	0.148	3.2	
nanoemulsion	total curcuminoids	240	36.7 ± 6.5	1	0.162	242.6	9.3
	curcumin	197	29.9 ± 5.1	1	0.156	210	9.8

[a]Data for C_{max} are presented as mean ± SEM (n=4).

significantly higher for the digested nanoemulsion than the intact nanoemulsion, suggesting that the classic digestion-diffusion route was still the primary absorption mechanism for curcumin in the nanoemulsion. However, more detailed in vivo experiments are needed to examine whether intact nanoemulsions are able to permeate across the gut wall, since only in the in vivo experiments the interaction of the nanoemulsion with the mucus layer and the M cells can be examined.[31]

Meanwhile, this work only examined the permeation rate of Tween 20 stabilized nanoemulsions. Since the coating of the lipid droplet may affect the interaction with Caco-2 cells and/or the epithelium lining the digestive tract, the effect of the surface properties of the nanoemulsions on the permeation rate and mechanism still remains elusive.

On the basis of the results in this work, the in vivo destinies of orally administered curcumin nanoemulsion and unformulated curcumin were compared in Figure 6. Inside the digestive

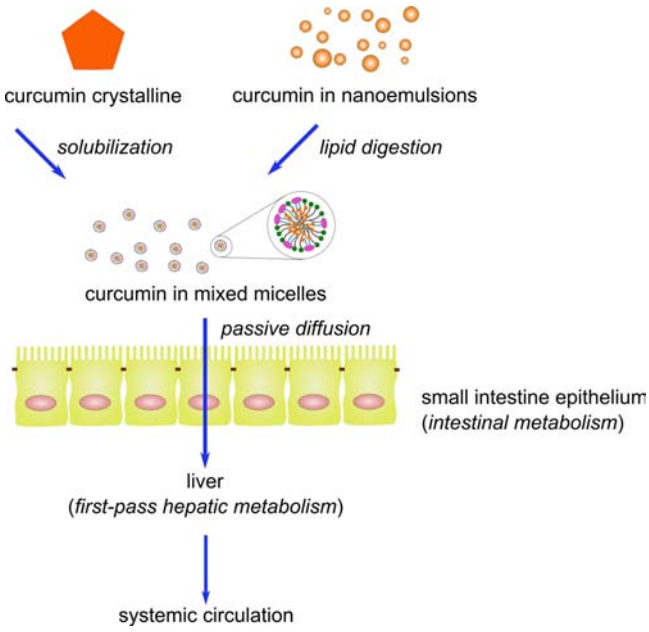

Figure 6. Scheme of the absorption and metabolism of unformulated (crystalline) curcumin and curcumin nanoemulsion.

tract, nanoemulsions undergo rapid digestion (lipolysis) and turn into free fatty acids and monoacylglycerols, both of which contribute to the mixed micelles in the small intestine lumen. Along with the lipolysis, curcumin that originally solubilized in the lipid phase gradually partitions in the mixed micelles. Subsequently, curcumin permeates across the small intestine epithelium by passive diffusion. After bypassing the liver, curcumin enters the systemic circulation and become bioavailable. Metabolism of curcumin may involve the intestinal metabolism and hepatic metabolism. In comparison, the permeation and metabolism of unformulated curcumin may be the same as the curcumin nanoemulsion. The key difference is that unformulated curcumin (crystalline) needs to be solubilized in the mixed micelle solution, which may be time and energy consuming. As we previously demonstrated, the extent of solubilization of curcumin crystalline in the mimic digestion environment is very limited.[26] Moreover, the pH of the major portion of the small intestine is from neutral to weak alkaline, under which, curcumin undergoes rapid degradation.[27] Therefore in this study, the difference in the curcumin solubilization results in the difference in the oral bioavailability.

Although, in principle, lipid digestion starts from the oral cavity and stomach, it primarily occurs in the small intestine. Therefore, this work, as many others, only used in vitro lipolysis assay to mimic the digestion in the small intestine.[32] Nevertheless, to stimulate the physicochemical change and digestion process of the formulation in the entire digestive tract, more sophisticated in vitro tests were probably required.

In summary, organogel-based nanoemulsions have been successfully developed for encapsulation and oral delivery of curcumin. The nanoemulsions revealed fast rate and high extent of digestion. The major permeation mechanism of curcumin in the nanoemulsion may be the classic digestion-diffusion. Furthermore, the oral bioavailability of curcumin in the nanoemulsion showed 9-fold improvement compared with the unformulated crystalline. This study demonstrated the application of organogel-based nanoemulsions in the oral delivery of lipophilic compounds, and provided a promising formulation platform for the delivery of poorly soluble nutraceuticals with high loading capacity and oral bioavailability in functional foods, dietary supplements, and pharmaceuticals applications.

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Notes

The authors declare no competing financial interest.

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