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Comparative Oral Absorption of Curcumin in a Natural Turmeric Matrix with Two Other Curcumin Formulations: An Open-label Parallel-arm Study

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Curcuminoids are the major bioactive molecules in turmeric, and poor bioavailability deters them from being the major components of many health and wellness applications. This study was conducted to assess the bioavailability of a completely natural turmeric matrix formulation (CNTMF) and compare its bioavailability with two other commercially available formulations, namely, curcumin with volatile oil (volatile oil formulation) and curcumin with phospholipids and cellulose (phospholipid formulation) in healthy human adult male subjects (15 each group) under fasting conditions. Each formulation was administrated orally as a single 500-mg dose in capsule form, and blood samples were analyzed by liquid chromatography mass spectrometry at various time intervals up to 24 h. The ingestion of the CNTMF was very well absorbed and resulted in a mean curcuminoids plasma C_{max} of 170.14 ng/mL (T_{max} = 4 h) compared with 47.54 ng/mL and 69.63 ng/mL for the volatile oil (T_{max} = 3 h) and phospholipid (T_{max} = 2.25 h) formulations, respectively. The extent of absorption of total curcuminoids in the blood for the CNTMF was 6× greater than volatile oil formulation and 5× greater than phospholipids formulation. The results of this study indicate that curcumin in a natural turmeric matrix exhibited greater bioavailability than the two comparator products. Copyright © 2017 John Wiley & Sons, Ltd.

Keywords: curcumin formulations; completely natural turmeric matrix; clinical trial; blood plasma absorption; phospholipid; turmeric oil.

INTRODUCTION

Extracts of curcuminoids generally contain curcumin (~77%) with small amounts of demethoxycurcumin (DMC, ~17%) and bisdemethoxycurcumin (BDMC, ~3%) (Sandur *et al*., 2007) that are the major bioactive components responsible for the pharmacological activities of turmeric (*Curcuma longa* L.) (Maheshwari *et al*., 2006). Numerous *in vitro* and *in vivo* studies indicate that curcuminoids have extensive biological activity against various diseases (Al-Karawi *et al*., 2016; Amalraj *et al*., 2017a; Daily *et al*., 2016; Gupta *et al*., 2013; Kocaadam and Sanlier, 2017; Kunnumakkara *et al*., 2017; Pulido-Moran *et al*., 2016; Tuorkey, 2014; Vaughn *et al*., 2016) Furthermore, turmeric extracts are among the top-selling herbal supplements (Andrew and Izzo, 2017).

Curcuminoids are amphiphilic in nature. They have higher solubility in organic solvents than in water, and the solubility of curcumin in aqueous solution is less than 0.03 μM in buffer at pH < 7 (Sahu *et al*., 2008). As a consequence, curcumin has low aqueous solubility and poor gastrointestinal absorption (Amalraj *et al*., 2017a; Douglass and Clouatre, 2015; Prasad *et al*., 2014a; Prasad *et al*., 2014b; Pulido-Moran *et al*., 2016). Furthermore, curcumin has a high rate of metabolism and metabolic inactivation (Al-Karawi *et al*., 2016; Gupta *et al*., 2013; Pulido-Moran *et al*., 2016; Ravichandran, 2013; Sahu *et al*., 2008) and rapid elimination from the body (Gupta *et al*., 2013; Prasad *et al*., 2014a; Prasad *et al*., 2014b) that leads to the conclusion that it has low bioavailability (Anand *et al*., 2007; Ravichandran, 2013). As a consequence, curcumin exhibits low serum levels and limited tissue distribution irrespective of route of administration due its poor absorption (Anand *et al*., 2007; Prasad *et al*., 2014a; Prasad *et al*., 2014b). The net result is that the poor absorption of curcumin limits its usefulness in general health care and as an adjunct in managing various diseases.

Various approaches have been investigated to overcome the poor absorption issues and enhance the utility of curcumin. The development of a delivery system that can enable efficient absorption of curcumin in a suitable medium at an appropriate dose will support the clinical applications of curcumin. In order to overcome the poor

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absorption, rapid metabolism, and poor bioavailability of curcumin, various pharmaceutical approaches have been developed. These include formulations with nanoparticles (Basniwal *et al*., 2011; Yallapu *et al*., 2012a; Yallapu *et al*., 2012b), liposomes (Chen *et al*., 2012; Liu *et al*., 2006; Ranjan *et al*., 2013), micelles (Kocher *et al*., 2014; Li *et al*., 2014; Schiborr *et al*., 2014; Wang *et al*., 2012), or interaction with macromolecules such as gelatin (Madhusudana Rao *et al*., 2015) and polysaccharides as galactomannans (Da-Lozzo *et al*., 2013) and cyclodextrin (Dhule *et al*., 2012; Mangolim *et al*., 2014; Yallapu *et al*., 2010). In addition, curcumin formulations involving hyaluronate vesicles and liposomes (Catalan-Latorre *et al*., 2016; Manca *et al*., 2015a) as well as polymer glycerosomes (Manca *et al*., 2015b) have been developed and studied. The absorption of various commercial curcuminoid products, including the phospholipid and volatile oil formulations used in the current study, has been compared on a relative mass efficiency basis (Douglass and Clouatre, 2015). Many of these technologies cannot accommodate high loading of curcuminoids that limits the amount of the finished product that is delivered, and some of the delivery systems are not readily suitable for food and supplement applications but may be used topically (Douglass and Clouatre, 2015).

A novel curcumin formulation inside a natural turmeric matrix has been developed that consists of a combination of hydrophilic and hydrophobic molecules (Amalraj *et al*., 2017b). Turmeric is fractionated into the isolated curcuminoids with 95% purity using food grade solvent ethanol, and the resulting oleoresin is crystallized to obtain curcuminoid powder. Powdered turmeric is extracted with water to obtain the water-soluble components including carbohydrates, dietary fiber, and total protein, while turmeric essential oil is separated by steam distillation. These three components are combined with the curcuminoids by a unique process of polar–nonpolar sandwich technology (publication number: US20160151440 A1) whereby curcuminoids are protected inside the resulting matrix. This matrix provides advantages such as enhanced physical stability, protection of the curcuminoids from degradation in the body, controlled curcuminoid release, and high absorbability. The composition of the product has been standardized, and the chemical composition is described in our earlier study (Amalraj *et al*., 2017b).

The bioavailability of curcumin from this natural matrix formulation was compared with unformulated 95% curcumin in a crossover study involving 12 healthy male subjects (Gopi *et al*., 2015). The C_{max} (ng/mL) for curcumin from the completely natural turmeric matrix formulation (CNTMF) and the unformulated product was 434.3 and 43.1, respectively. The curcumin area under the curve (AUC) (ng mL/h) for the CNTMF and unformulated product was 904.0 and 165.7, respectively. Therefore, the C_{max} and AUC for the CNTMF relative to the unformulated 95% curcumin were approximately 10-fold and 5.5-fold, respectively, demonstrating a much greater bioavailability for the novel formulation.

The aim of this study was to compare the absorbability and plasma levels of total curcuminoids of three different commercially available formulations in healthy male adults after a single 500-mg oral dose, the dose normally recommended for each of the three products. The novel inside the CNTMF was compared with a formula consisting of curcuminoids with turmeric essential oil from turmeric rhizome (volatile oil formulation) and a formula that contained curcuminoids with lecithin and cellulose (phospholipid formulation). These latter two formulations are the most commercially available formulations as 500-mg capsules, and therefore, the bioavailability of the CNTMF was compared with these two formulas at their most commonly used dosage and dosage form. In order to determine relative bioavailabilities, the data were normalized on the basis of milligrams of curcumin in each product.

MATERIALS AND METHODS

The CNTMF was obtained from Aurea Biolabs (P) Ltd, Cochin, India, and is marketed as Cureit™/Acumin™. The volatile oil and phospholipid formulations were purchased from Amazon online. The curcumin volatile oil formulation is marketed as 'Curcu-Gel Ultra' (expiration date: August 2016), and curcumin phospholipid formulation is available as 'Doctor's Best Curcumin Phytosome' (expiration date: March 2016). The curcuminoid contents in all samples were determined by high-performance liquid chromatography dual mass spectrometry (USP36-NF31, 2013; Xiu-Mei *et al*., 2012). The CNTMF contained 46.5% total curcuminoids (curcumin: 36.0%, DMC: 9.0%, and BDMC: 1.5%), 43% total carbohydrates, 5% fiber, 2.4% proteins, and 3.2% volatile oil that mainly consists of aromatic turmerone, dihydroturmerone, turmeronol, curdione, and bisacurone (Amalraj *et al*., 2017b). The volatile oil formulation contained 85.9% curcuminoids (curcumin: 70.2%, DMC: 14.3%, and BDMC: 1.4%) with 7–9% essential oil that is naturally present in turmeric, and the phospholipid formulation contained 19.8% curcuminoids (curcumin: 16.1%, DMC: 3.2%, and BDMC: 0.5%) with 40% phospholipids and 40% microcrystalline cellulose.

Subjects received a single oral 500-mg dosage of one of the products in capsule form. Curcumin, DMC, and BDMC were purchased from Sigma-Aldrich for the standardizations. Based on this analysis, the amounts of curcumin in 500 mg of the turmeric matrix, volatile oil, and phospholipid formulas were 180, 351, and 80.5 mg, respectively.

Ethics and approvals. This study was conducted at Agile Pharma Services, Bangalore, India, and the research was carried out in accordance with the principles of the Declaration of Helsinki (ethical principles for medical research involving human subjects, revised by the World Medical Association general assembly, Seoul, October 2008), 'International Conference on Harmonization Good Clinical Practice', national regulations (Indian Council of Medical Research guidelines), 'Note for guidance on the investigation of bioavailability and bioequivalence, EMEA 2001', 'Indian Good Clinical Practice', and 'Schedule Y' of Indian drugs and cosmetics act. Participants were informed of the details of the study prior to signing a consent form.

All study-related documents were reviewed by the Independent Ethics Committee of Clinicom, Bangalore, India, and approved on 25 August 2015. The protocol was registered with Clinical Trials Registry India (clinicaltrials.gov) (CTRI/2016/07/007118). The study was in compliance with part 56 of title 21 of the Code of Federal Regulations and International Conference on Harmonization guidelines.

Inclusion and exclusion criteria of participants. Fifty-one normal adult male volunteers between 18 and 45 years of age were initially screened for the study. Forty-five subjects who met the inclusion criteria gave written informed consent and were included in the study. A power calculation indicated that this number of subjects was adequate for the study. All volunteers had a body mass index of 18.5 to 24.9 kg/m^2, and no evidence of underlying disease during the pre-study screening, medical history, physical examination, and laboratory investigations performed within 21 days prior to commencement of the study. Pre-study screening blood parameters included red blood cell, aspartate aminotransferase, alanine aminotransferase, bilirubin, urea, creatinine, potassium, sodium, and laboratory parameters as urine glucose, systolic blood pressure, electrocardiogram, and chest X-ray were within normal limits or were considered by the investigator to be of no clinical significance with respect to participation in the study. All subjects tested negative for hepatitis B and C and were negative or nonreactive for antibodies to human immunodeficiency virus 1 and 2.

The exclusion criteria included individuals who were allergic to curcumin or any component of the formulation or any other related drug and had a history or presence of significant cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic, neurological, or psychiatric disease. Individuals who exhibited alcohol dependence, alcohol abuse or drug abuse, and history of chronic smoking (10 or more units per day of cigarettes, bidis, or any other form), or chronic consumption of tobacco products also were excluded.

Study procedure. The 45 healthy male volunteers were divided randomly into equal three groups for each formulation using an online randomization program (http://www.randomization.com). Vital signs (blood pressure, pulse rate, respiratory rate, and oral temperature) were measured before check-in, prior to dosing on the dosing day, and at 2, 4, 6, 12, and 24 h post-dose in each study group. All measurements (except check-in and pre-dose vital signs examinations) were performed within ±1 h of the scheduled time so as not to interfere with scheduled blood sampling times or meals. The actual time of measurement was recorded in the respective subject's case report form.

Subjects were asked about their well-being before check-in, prior to dosing on the dosing day and approximately at 2, 4, 6, 12, and 24 h post-dose. In addition, at all times, subjects were asked to report any side effects spontaneously to the monitoring staff. Any reports were recorded in the case report form. Subjects were provided dinner on the pre-study day and thereafter fasted overnight (for at least 10 h before dosing) as well as for 4 h after dosing. Water was not permitted 1 h before and 1 h after product administration, but was allowed at all other times *ad libitum*.

Each subject was administered 500 mg of the assigned formulation orally with 240 mL water as determined by the randomization schedule (15 subjects per group), and a mouth check was conducted to ensure compliance. Subjects were not aware of the name of the product being consumed. There were no co-interventions involved in the study and no intent to treat analysis. After dosing, lunch, snacks, and dinner were served at 4, 8, and 12 h, respectively, from the time of dosing. The meal plan was identical for all group subjects. The baseline characteristics of the test individuals before sample administration are shown in Table 1. There were no dropouts with all 45 subjects completing the study.

Sample collection. Each pre-dose blood sample (6 mL) was collected within 1 h before dosing, and a total of 19 (6 mL each) blood samples were collected. The post-dose samples (6 mL) were collected at 0.25, 0.50, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3, 4, 6, 8, 10, 12, and 24 h after dosing into vacuum tubes containing K_2EDTA.

Table 1. The baseline characteristics of the study subjects before sample administration

Variables	CNTM formulation (n = 15)	Volatile oil formulation (n = 15)	Phospholipid formulation (n = 15)	Total (n = 45)
Age (years)	22.7 ± 2.3	24.2 ± 4.9	27.3 ± 8.8	24.7 ± 6.1
Body height (cm)	165.0 ± 9.2	166.8 ± 6.4	160.1 ± 6.4	164.0 ± 7.8
Body weight (kg)	64.4 ± 13.9	63.0 ± 8.8	64.9 ± 11.6	64.1 ± 11.4
Pulse rate (bpm)	70.1 ± 15.9	73.7 ± 1.4	73.0 ± 1.3	72.3 ± 9.2
Hemoglobin (%)	15.4 ± 1.2	15.3 ± 1.0	15.2 ± 1.2	15.3 ± 1.1
White blood cell (cells/cumm)	8273 ± 1962	9653 ± 1664	9073 ± 1420	9000 ± 1754
Red blood cell (milli/cumm)	5.2 ± 0.4	5.1 ± 0.6	5.3 ± 0.3	5.2 ± 0.5
Urea (mg/dL)	23.6 ± 6.0	20.9 ± 6.5	21.1 ± 5.4	21.9 ± 6.0
T-cell count	147.2 ± 32.3	155.7 ± 28.8	159.3 ± 39.1	154.1 ± 33.3
Creatinine (mg/dL)	0.9 ± 0.1	1.0 ± 0.1	0.9 ± 0.2	1.0 ± 0.1
Alkaline phosphatase (U/L)	194.1 ± 60.7	228.7 ± 70.7	235.4 ± 39.8	219.4 ± 60.0
Protein (g/dL)	7.1 ± 0.3	7.1 ± 0.4	7.5 ± 0.4	7.2 ± 0.4
Potassium (mEq/L)	3.8 ± 1.2	4.1 ± 0.3	3.9 ± 0.3	3.9 ± 0.7
Sodium (mEq/L)	139.8 ± 2.4	140.9 ± 1.8	139.7 ± 1.9	140.2 ± 2.1

Each value is the mean ± SD. There is no statistical significant difference between the groups. CNTM, completely natural turmeric matrix.

The heparin-lock technique was used to prevent clotting of blood in the indwelling cannula. Before each blood sample was drawn, 0.5 mL of blood was discarded to prevent the saline diluted blood and heparin from interfering with the analysis. The total volume of blood drawn including the volume necessary for the screening (12 mL), and the volume of blood discarded (0.5 mL) did not exceeded 136 mL per subject for the entire study. No extra blood samples were collected for repeat laboratory tests.

Sample separation and preparation. After collection, all blood samples were stored and transferred in a container precooled with refrigerant gel packs and subsequently centrifuged at 3500 rpm at 4 °C for 10 min within 60 min of collection. After centrifugation, the separated plasmas were transferred into suitably labeled polypropylene tubes.

Each sample of plasma was extracted with ethyl acetate (3.0 mL) at room temperature. The organic layer was filtered, and 1.0 mL aliquots were pipetted into evaporation tubes. The solvents were evaporated using a nitrogen stream, 2.0 mL of methanol was used to dissolve each sample, and the samples were analyzed by a validated liquid chromatography mass spectrometry system (Xiu-Mei *et al*., 2012).

Analytical methods. The liquid hromatography mass spectrometry consisted of an Acquity High Performance LC (Waters Corporation) and electrospray ionization mass spectrometer (Xevo TQD, Waters Corporation). Positive mode electrospray ionization mass spectrometry was performed with capillary (3.0 kV) and cone (34 V) voltages, drying gas (N2) flow rate set at 600 L/h, ionization sources at 150 °C, and the desolvation temperature at 500 °C. Multiple reaction monitoring, using the precursor to product combination of *m/z* 369 to 177.0, *m/z* 339 to 147, and *m/z* 309 to 147 was used to quantify curcumin, DMC, and BDMC, respectively. The samples were separated on an Waters AQUITY BEH C18 column (2.1 × 50 mm, 1.7 μm) (Milford, MA USA) using formic acid (0.1%, A)/acetonitrile (B) as the mobile phase with the following profile: 0–0.5 min, 60% A; 0.5–1.2 min, 10% A; 1.2–1.8 min, 5% A; and 1.8–3.0 min, 60% at the flow rate of 0.6 mL/min. The limit of detection of the instrument was 1 ppb, and the limit of quantification of the method was 10 ppb. Total curcuminoids were quantitated by using a calibration graph obtained from each curcuminoid (curcumin, DMC, and BDMC) standards, and the total curcuminoids in each sample were assigned in comparison with sum of the each standard curcuminoids.

Statistical analysis. Pharmacokinetic parameters including C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ and T_{max} for all three investigational product groups were generated using WINNONLIN version 5.0.1. The pharmacokinetic parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were analyzed using the general linear model analysis of variance with the main effect of treatment. Statistical analyses were performed using a SAS® package (SAS Institute Inc., Cary NC, USA). Values with $p < 0.05$ were considered statistically significant.

RESULTS

This study involved a randomized, open-label, three treatment groups, and parallel comparative design to assess the single-dose (500 mg) oral bioavailability of three curcumin formulations in 45 healthy volunteers under fasting conditions. No adverse effects were reported by the subjects taking any of the three products. The effects of a novel formulation of curcumin (CNTMF) were compared with volatile oil and phospholipid containing formulations. Pharmacokinetic parameters of curcuminoid concentrations by mean AUC ± standard deviation, maximum and minimum absorbance for each time interval, and median (all concentrations in ng/mL) for each formulation at the different time intervals up to 24 h are given in Table 2. The AUC is the most reliable measure of the biological availability because it measures the entire response over time and provides a more accurate picture of bioavailability. The C_{max} represents only one point in time and is therefore less robust (Stahl *et al*., 2002).

From Table 2, it is evident that the maximum absorption for the CNTMF was approximately 366 ng/mL at the fourth hour, whereas for the volatile oil formulation, maximum absorption was 104 ng/mL at 2.75 h, and for the phospholipid formulation, it was 138 ng/mL at 2.5 h. The T_{max} time points were not statistically different.

The graphical representations of the mean concentrations of the three formulations as a function of time are presented in Fig. 1. Multiple curcuminoid concentration peaks were observed in the plasma as a function of time for the all three formulations that are discussed in the next section. The total average pharmacokinetic variables (mean ± standard deviation) for each formulation calculated from plasma total curcuminoids as well as the *p*-values are given in Table 3. The maximum plasma total curcuminoids (C_{max}) and the AUC for the CNTMF were approximately 170 and 825 ng/mL, respectively. In comparison, these values for the volatile oil formulation were approximately 48 and 117 ng/mL, respectively, and for the phospholipid formulation were approximately 70 and 187 ng/mL, respectively (Table 3 and Fig. 1).

The parametric lower and upper 90% confidence intervals for the ratio between the CNTMF and the volatile oil and phospholipid formulations were above 125% for the log-transformed pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} under fasting conditions. Hence, it can be concluded from the earlier results that the bioavailability of the CNTMF is significantly greater ($p < 0.01$) than the volatile oil and phospholipid formulations. The absorption of the CNTMF was approximately 7× greater than the volatile oil formulation in terms of absorption (AUC_{0-t}) and 3.6× greater in terms of the rate of absorption (C_{max}). The extent of absorption of the CNTMF based on the AUC_{0-t} and $AUC_{0-\infty}$ was 4.4 and 6.8× greater (5.6× average), respectively, as compared with the phospholipid formulation. Similarly, the rate of absorption (C_{max}) was 2.5× higher.

DISCUSSION

As noted in Fig. 1, multiple curcuminoid concentration peaks were observed in the plasma for the matrix

Table 2. Curcuminoid concentrations (in ng/mL) in plasma expressed as mean, median, maximum, and minimum concentrations for each group of 15 subjects for each formulation at various time intervals

	Mean ± SD			Minimum			Maximum			Median		
Time (h)	CNTM formulation	Volatile oil formulation	Phospholipid formulation	CNTM formulation	Volatile oil formulation	Phospholipid formulation	CNTM formulation	Volatile oil formulation	Phospholipid formulation	CNTM formulation	Volatile oil formulation	Phospholipid formulation
0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.25	50.9 ± 47.8	25.9 ± 15.4	42.7 ± 48.9	2.30	3.50	1.00	141.7	52.40	186.8	32.2	24.9	26.7
0.50	64.5 ± 70.3	17.8 ± 11.1	20.6 ± 27.7	1.80	3.80	1.00	282.5	38.90	113.3	43.0	17.4	10.2
0.75	44.9 ± 66.6	12.0 ± 10.6	9.60 ± 9.00	5.40	1.10	0.10	267.4	35.10	26.20	19.8	10.1	7.40
1.0	17.4 ± 10.2	9.00 ± 7.90	8.70 ± 9.10	3.00	0.30	0.90	35.90	23.70	32.60	15.2	6.00	4.60
1.25	16.4 ± 13.4	6.40 ± 6.90	9.60 ± 8.00	0.20	0.10	0.10	49.70	18.90	25.40	17.3	4.50	8.20
1.50	17.8 ± 15.6	3.45 ± 3.20	11.2 ± 10.9	0.90	0.60	0.80	54.90	11.30	34.20	13.9	1.90	5.10
1.75	21.5 ± 20.9	4.10 ± 2.40	14.5 ± 15.7	0.20	0.40	0.20	74.30	8.00	56.70	15.4	4.00	12.0
2.0	34.8 ± 30.0	5.10 ± 3.80	18.0 ± 21.9	0.10	0.10	0.50	99.30	12.90	75.50	30.3	4.30	9.20
2.25	46.8 ± 56.4	7.50 ± 5.40	25.7 ± 22.4	0.30	0.30	0.50	225.8	17.80	77.40	31.6	6.10	23.3
2.5	73.1 ± 87.7	11.2 ± 7.60	33.0 ± 35.9	2.10	0.30	1.20	303.0	22.30	138.1	36.7	8.90	19.4
2.75	63.4 ± 71.2	26.2 ± 23.6	29.2 ± 38.1	1.40	7.50	2.00	278.9	104.3	117.3	51.8	20.1	15.8
3.0	81.7 ± 99.9	38.3 ± 24.6	27.1 ± 24.3	9.70	7.70	0.50	365.5	101.9	68.60	35.8	39.8	19.8
4.0	74.1 ± 84.8	16.9 ± 13.6	18.2 ± 20.9	0.90	2.90	0.10	251.1	52.00	70.60	38.7	12.7	9.30
6.0	70.2 ± 59.7	9.30 ± 6.20	12.9 ± 21.7	0.70	0.70	0.50	198.0	22.00	85.50	58.9	7.90	5.00
8.0	58.4 ± 45.1	6.40 ± 7.50	18.9 ± 41.9	2.50	0.40	0.70	137.8	28.10	151.9	47.3	3.80	2.60
10.0	46.4 ± 36.2	1.80 ± 2.00	8.50 ± 18.7	2.40	0.00	0.10	97.60	7.30	58.4	38.2	0.90	1.60
12.0	23.9 ± 22.2	0.40 ± 0.60	0.80 ± 1.10	0.90	0.00	0.00	70.70	1.90	4.10	20.6	0.00	0.40
24.0	5.70 ± 7.50	0.10 ± 0.20	0.40 ± 0.90	0.00	0.00	0.00	24.10	0.60	3.50	1.30	0.00	0.10

CNTM, completely natural turmeric matrix.

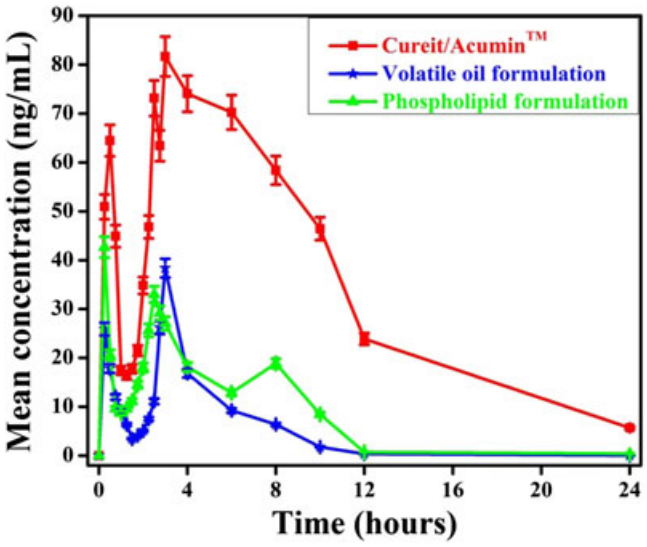

Figure 1. Mean plasma concentration (ng/mL) of curcuminoids from completely natural turmeric matrix formulation (Cureit™/Acumin™), compared with volatile oil and phospholipid formulations. All the values reported are mean ± SD (n = 15). [Colour figure can be viewed at wileyonlinelibrary.com]

formulation as well as the volatile oil and phospholipid formulations. These peaks are due to initial portal and lymphatic uptake followed by rapid metabolism with subsequent entero-hepatic recycling of curcumin glucuronide and sulfate (Kocaadam and Sanlier, 2017; Prasad *et al*., 2014a). The detection of these peaks may reflect the use of highly sensitive analytical methods used in the current study. Furthermore, the very large peak for the CNTMF study product at approximately 8 h post-administration and beyond may be a reflection of its novel bioavailability characteristics. Similar results involving multiple peaks following curcumin administration have been previously obtained for various formulations by several other investigators (Antony *et al*., 2008; Sunagawa *et al*., 2015). Failure by other investigators to detect multiple peaks may be due to factors including the type of product formulation, sensitivity of the assay, the extraction procedure, the time points selected, and the dose administered.

As can be seen from Table 2 and Fig. 1, measurable blood levels of the curcuminoids were not detected after the 12-h time point for the volatile oil and phospholipid formulations but were evident at the 24-h time point for the CNTMF. The failure to detect curcuminoids after 12 h may have been due to the much lower absorption from the phospholipid and volatile oil products, rapid metabolism and removal from the blood, and the lower amount of curcuminoids present in 500 mg of the phospholipid formulation.

The results in Table 3 indicate that when 500 mg of each of the three formulations is administered as a single dose, the standard recommended dose for each, the bioavailability of the CNTMF as compared with the volatile oil formula and the phospholipid formula based on average AUCs was approximately 7.3-fold and 5.6-fold greater, respectively. The bioavailability of curcumin from the volatile oil formulation and the phospholipid formulation have been compared with standard 95% curcumin and have been shown to exhibit absorptions of approximately 6.25-fold and 20-fold greater, respectively (Douglass and Clouatre, 2015).

Douglass and Clouatre (2015) compared the relative mass efficiency of a number of curcumin formulations with increase plasma levels of total curcuminoids. The use of relative mass efficiency allows comparison of the absorbability and bioavailability of different formulations that vary in their weight percentage of curcuminoids, as is the case in the current comparative study. The data are normalized based on relative mass absorption. Two of the formulations that were included in the comparison of Douglass and Clouatre (2015) were products that were used in this study in comparison with the CNTMF, namely, the curcumin volatile oil and phospholipid formulations. The phospholipid formula versus the volatile oil formula was reported to exhibit a relative mass efficacy of 1.3:1. The current study did not use the relative mass efficiency calculation of Douglass and Clouatre (2015) but rather normalized the data based on milligrams of curcumin administered. When one averages the AUC_{0-t} and $AUC_{0-\infty}$ for these two products on this basis, the ratio is 1.36:1, agreeing very well with the previous calculation.

It is difficult to make pharmacokinetic comparisons between curcumin formulations that contain differing amounts of curcumin, have markedly differing amounts of total product mass, and exhibit wide variations in the absorption of curcumin. Table 4 summarizes published pharmacokinetic data from studies with various formulations including micronized curcuminoids plus turmeric oil (BCM-95®), curcuminoids formulated with phosphatidylcholine from soy lecithin and microcrystalline cellulose (Meriva®), complexed with a hydrophobic carrier, cellulosic derivatives, and natural antioxidants (CurcuWIN®), complexed with γ-cyclodextrin (Cavacurmin®), a solid lipid curcumin particle (Longvida®), and a micellar formulation. The data are compared on the basis of C_{max} per mg curcumin and

Table 3. The average PK variables (mean ± SD) from plasma total curcuminoids of the three formulations and the *p*-value

PK parameter	CNTM formulation	Volatile oil formulation	Phospholipid formulation	*p*-value
AUC_{0-t} (ng mL/h)	824.9 ± 466.5	117.3 ± 56.8	187.3 ± 190.9	<0.01*
$AUC_{0-\infty}$ (ng mL/h)	812.2 ± 559.6	105.3 ± 40.3	120.1 ± 61.6	<0.01*
C_{max} (ng/mL)	170.14 ± 104.6	47.54 ± 26.4	69.63 ± 51.1	<0.01*
K_{el} (1 per h)	0.26 ± 0.26	0.34 ± 0.34	0.33 ± 0.33	0.1726
T_{half} (h)	3.51 ± 2.3	3.30 ± 3.2	4.13 ± 4.1	0.2948
T_{max} (h)	3.72 ± 2.6	3.00 ± 1.7	2.63 ± 2.4	0.1274

CNTM, completely natural turmeric matrix; PK, pharmacokinetic.

*Statistically significant.

Table 4. Comparison of pharmacokinetic properties of various curcumin formulations expressed per mg of administered curcumin

Source	Curcumin dose (mg)	C_{max} (ng/mL)	C_{max} per mg curcumin	AUC (ng mL/h)	AUC per mg curcumin	Reference
Acumin™	180	170	0.94	825	4.58	Current
Acumin	190	434	2.28	904	4.75	Gopi *et al*. (2015)
95% curcumin	500	43.1	0.086	166	0.330	Gopi *et al*. (2015)
95% curcumin	2920	57	0.014	731	0.250	Asher *et al*. (2017)
95% curcumin	1900	150	0.079	462	0.243	Antony *et al*. (2008)
BCM-95®	351	47.5	0.334	117	0.14	Current
BCM-95	278	45	0.160	NA	NA	Sunagawa *et al*. (2015)
BCM-95	376	10.9	0.029	1.1	0.003	Jager *et al*. (2014)
BCM-95	1116	457	0.409	3201	2.87	Antony *et al*. (2008)
Meriva®	80.5	69.9	0.865	187	2.33	Current
Meriva	612	344	0.562	3975	6.50	Antony *et al*. (2008)
Meriva	376	65.3	0.174	8.7	0.023	Jager *et al*. (2014)
Meriva	385	529	1.374	669	1.78	Asher *et al*. (2017)
CucuWin®	376	34.9	0.093	380	1.01	Jager *et al*. (2014)
Cavacurmin®	371	87	0.234	389	1.05	Purpura *et al*. (2017)
Longvida®	650	22.4	0.034	95.3	0.147	Gota *et al*. (2010)
Micelles	410	162	0.390	450	1.10	Schiborr *et al*. (2014)

NA, not available.

AUC per mg curcumin administered from the various pharmacokinetic studies. Results involving these formulations are also compared with the results from the current study involving the novel CNTMF (Acumin™), the volatile oil (BCM-95), and phospholipid (Meriva) formulations. Published data are also presented for unformulated 95% curcumin.

If one uses the average C_{max} per mg curcumin and AUC per mg curcumin for the CNTMF study product as compared with the averages for unformulated 95% curcumin, the values for the CNTMF are approximately 9-fold and 17-fold greater, respectively. When one makes this comparison between the CNTMF with the average values for turmeric oil (BCM-95), the C_{max} per mg curcumin for the novel CNTMF study product is approximately 6.9-fold greater, while the AUC per mg curcumin is approximately 4.7-fold greater. A similar comparison with phosphatidylcholine formulated curcumin (Meriva) indicates that the C_{max} per mg curcumin for the CNTMF product was approximately 2.2-fold greater while the AUC per mg curcumin consumed was approximately 1.8-fold greater (Table 4).

CurcuWIN is another absorption-enhanced product that is composed of 20% curcumin, a hydrophilic carrier, cellulose derivatives, and antioxidants (Jager *et al*., 2014). When the C_{max} per mg curcumin of this product is compared with that of the CNTMF used in this study, the CNTMF produced a maximum concentration that was approximately 17.3-fold greater per mg of curcumin. When comparing the AUC per mg curcumin administered, the value for the CNTMF study product versus CurcuWIN was approximately 4.6-fold greater (Table 4).

When the CNTMF product is compared with curcumin complexed with γ-cyclodextrin (Cavacurmin) (Purpura *et al*., 2017), the C_{max} per mg and AUC per mg consumed curcumin for the novel study product were approximately 6.8-fold and 4.4-fold, respectively, greater for the novel CNTMF product (Table 4). Similarly, when comparing the pharmacokinetic properties of a solid lipid curcumin particle (Longvida) (Gota *et al*., 2010) with the study product, the C_{max} per mg curcumin and AUC per mg administered curcumin were approximately 47-fold and 32-fold greater for the CNTMF, respectively. Finally, when comparing these values for a micellar product (Schiborr *et al*., 2014) with the CNTMF, the C_{max} per mg curcumin and AUC per mg curcumin for the CNTMF were approximately 4.1-fold and 4.2-fold greater, respectively (Table 4).

In summary, the C_{max} and AUC per mg of curcuminoids in all other studies (Table 4) exhibited lower values, indicating that the CNTMF study product is more bioavailable than the other formulations. Although wide variations exist in the data from the Meriva and BCM-95 pharmacokinetic studies, the results indicate that the CNTMF formula exhibits greater bioavailability than these two products. Differences in sensitivity and specificity of the assay methods may be responsible for these widely varying results. Furthermore, differences in doses given, manner of administration (with or without food), sample storage conditions, extraction procedures, and how endpoints were calculated may also contribute to the variations in the results.

Limitations of the current study are the fact that only male subjects were used, and the study was randomized but not crossover in design. In addition, the amount of total curcuminoids in 500 mg of each of the three products differs, which constitutes a limitation of the study. However, to account for the differences in the curcumin content in various formulations, the data were normalized on the basis of C_{max} per mg curcumin and AUC per mg curcumin that was administered. The volatile oil and phospholipid formulations are the most available products in the market in the form of 500-mg capsules. When one normalizes the AUC_{0-t} based on the amount of total curcuminoids administered in the 500-mg dose of each of the three products, the AUC for the CNTMF is approximately 4.7-fold greater than for the volatile oil formulation and 1.8-fold greater than for the phospholipid formulation per mg of total curcuminoids.

Therefore, the data indicate that the CNTMF exhibits greater absorption as compared with the other two formulas used in this study, with a much greater bioavailability as compared with various other absorption-enhanced curcumin products (Table 4).

CONCLUSIONS

This novel CNTMF facilitates the absorption and bioavailability of curcumin as compared with phospholipid and volatile oil formulations. Normalization of the data on the basis of AUC per mg administered curcumin indicates that the CNTMF also exhibits greater bioavailability as compared with various other curcumin formulations. The solubility and absorbability of CNTMF were enhanced by the combination of curcuminoids with highly polar (proteins, fibers, and polysaccharides) and nonpolar (curcumin essential oil) entities derived from turmeric, resulting in a natural turmeric complex matrix.

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Conflict of Interest

Eight of the authors (S. G., J. J., K. V., S. J., A. A., A. C. A., R. G., and T. R. S.) are employed by Aurea Biolabs Ltd, a subsidiary of Plant Lipids Ltd. The other authors (C. D., A. B. K., and S. J. S.) have no conflict of interest.

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