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Safety and Pharmacokinetics of a Solid Lipid Curcumin Particle Formulation in Osteosarcoma Patients and Healthy Volunteers

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Curcumin is the lipid-soluble antioxidant compound obtained from the rhizome of *Curcuma longa* Linn, also known as turmeric. Curcumin targets multiple chemotherapeutic and inflammatory pathways and has demonstrated safety and tolerability in humans, supporting its potential as a therapeutic agent; however, the clinical literature lacks conclusive evidence supporting its use as a therapeutic agent due to its low bioavailability in humans. The purpose of this study was to quantify plasma levels of free curcumin after dosing of a solid lipid curcumin particle (SLCP) formulation versus unformulated curcumin in healthy volunteers and to determine its tolerability and dose−plasma concentration relationship in late-stage osteosarcoma patients. Doses of 2, 3, and 4 g of SLCP were evaluated in 11 patients with osteosarcoma. Plasma curcumin levels were measured using a validated high-performance liquid chromatography method. The limit of detection of the assay was 1 ng/mL of curcumin. In healthy subjects, the mean peak concentration of curcumin achieved from dosing 650 mg of SLCP was 22.43 ng/mL, whereas plasma curcumin from dosing an equal quantity of unformulated 95% curcuminoids extract was not detected. In both healthy individuals and osteosarcoma patients, high interindividual variability in pharmacokinetics and nonlinear dose dependency was observed, suggesting potentially complex absorption kinetics. Overall, good tolerability was noted in both healthy and osteosarcoma groups.

KEYWORDS: *Curcuma longa*; solid lipid curcumin particle; bioavailability; pharmacokinetics; safety; osteosarcoma

INTRODUCTION

Curcumin (1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione or diferuloylmethane, is a lipid-soluble antioxidant compound from *Curcuma longa* Linn. or turmeric rhizome. Turmeric powder is used as a cooking spice, food preservative, and natural yellow food coloring in Asia, Europe, and America and is also integral to traditional medicinal systems, such as Ayurveda in India. The powder of turmeric root sold as spice contains 0.5−3% curcumin by weight (*1*).

Curcumin modulates expression of genes involved in cell proliferation, cell invasion, metastasis, angiogenesis, and resistance to chemotherapy (*2*, *3*). It is a potent inhibitor of the activation of various transcription factors including COX-2, nuclear factor-κB (NF-κB), activated protein-1 (AP-1), signal transducer and activator of transcription (STAT) proteins, peroxisome proliferator-activated receptor-γ (PPAR-γ), and β-catenin (*4*). Curcumin also down-regulates cyclins D1 and E and MDM2 and up-regulates p21, p27, and p53 (*5*).

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Osteogenic sarcoma (osteosarcoma) is a primary malignant tumor of the bone. Although it can occur at any age, it usually affects children and young adults and has one of the lowest survival rates of any pediatric cancer. Treatment is usually a combination of surgery and chemotherapy, with subsequent relapse rate of up to 40% at 3 years (*6*). Curcumin, which targets multiple chemotherapeutic pathways and possesses good tolerability, is a potential target for primary or adjunct treatment of osteosarcoma (*7*, *8*). Curcumin causes a dose-dependent growth inhibition of osteosarcoma cells and accumulation of cells in the G(2)/M phase of the cell cycle, with half-maximal growth inhibitory concentration ranging from 14.4 to 24.6 μM in seven osteosarcoma cell lines tested (*7*). However, the bioavailability of curcumin in children and young adults with late-stage cancer is poorly understood.

Preclinical data have shown that curcumin can both inhibit the formation of tumors in animal models of carcinogenesis and act on a variety of molecular targets involved in cancer development (*8*). Curcumin has been proved effective in inhibiting tumor growth in xenograft models (*9*, *10*). Despite the promise of curcumin shown in animal models, null outcomes in the clinic are thought to be due to curcumin's water insolubility, low

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bioavailability, and inability to reach required blood concentrations necessary to affect disease markers or clinical end points, even with chronic dosing of up to 12000 mg per day (*11*). In prior work, following an 8000 mg dose of 95% curcuminoids, curcumin was detected only as its glucuronide and sulfate conjugates (*12*). However, a focus on quantifying free versus conjugated (i.e., glucuronidated) forms of curcumin in biological fluids represents a heightened focus on translational research, because glucuronidated and sulfated forms of curcumin appear to offer low activity, low cell permeability, and short plasma half-life compared to the free form (*13*−*15*). Concentrations of at least 0.10 μM (∼37 ng/mL) free curcumin reversed disease state and reduced IL-1b in Alzheimer's disease models, which shares similar inflammatory markers with osteosarcoma (*16*, *17*). However, several clinical studies have failed to show detectable levels of curcumin in plasma. The purpose of this study was to determine if therapeutic levels of the free form of curcumin in plasma could be detected after the administration of a single dose of optimized lipidated curcumin formulation to healthy volunteers and to late-stage osteosarcoma patients and to observe the tolerability and safety of the formulation after a single administration.

MATERIALS AND METHODS

Chemicals and Reagents. Solid lipid curcumin particle (SLCP) was obtained from M/s Pharmanza Herbals Pvt Ltd. (PHPL) Gujarat, India, and manufactured under license from Verdure Sciences, Noblesville, IN, under the brand name LONGVIDA (M3C-X). A 95% curcuminoids extract was obtained from Pharmanza Herbals. HPLC grade acetonitrile and methanol were purchased from Rankem (New Delhi, India). HPLC grade triethylamine, acetic acid, and phosphoric acid were purchased from Merck (Darmstadt, Germany).

Solid Lipid Curcumin Particle. Multiple lots of SLCP were produced using patent-pending methodology (University of California, Los Angeles (UCLA)). Turmeric root extract containing curcumin was mixed with soy lecithin containing purified phospholipids, docosahexaenoic acid (DHA) and/or vegetable stearic acid, ascorbyl (vitamin C) esters, and inert ingredients. The formulation was manufactured under cGMP standards and met internal and external specifications for precise chemical and physical characteristics deemed to be suitable by bioavailability-guided product development. Curcumin content of the formulation was in the range of 20−30%.

Human Trials. *Osteosarcoma Patients*. Eleven patients of Indian descent (7 men and 4 women), ages 12−60 years (average age = 18.3 and average weight = 45.1 kg), who were diagnosed with metastatic high-grade osteogenic sarcoma and had exhausted all standard treatment options, were recruited under a Human Ethics Committee (HEC) approved clinical study protocol at Tata Memorial Hospital, Mumbai, India (**Table 1**). Patients were enrolled over a period of 8 months between August 2008 and March 2009. Written informed consent was obtained from all patients prior to enrollment in the study. SLCP was also approved by the Drugs Controller General of India.

The subjects were educated on food sources of curcumin and asked to avoid all foods containing curcumin for 1 day before dose administration. Subjects fasted for at least 10 h before administration and for 1 h after administration of the study drug. SLCP was administered in a capsule in oral dosages of 2000 mg (containing 400−600 mg of curcumin), 3000 mg, and 4000 mg curcumin formula, with 8 oz of water over a maximum duration of 5 min. These doses were selected on the basis of preliminary animal and human pharmacokinetic data in healthy subjects (data not shown). A minimum of three subjects per cohort was planned, and patients were enrolled in the higher dose cohort once the immediately lower dose cohort completed recruitment. Blood samples (5 mL) were collected in EDTA tubes before dosing and at 1, 2, 3, 4, 5, 6, 7, 8, 10, and 12 h after administration. All protocol procedures were performed at the Advanced Centre for Treatment, Research and Education in Cancer (ACTREC). The plasma was separated from blood immediately after collection and kept at −20 °C until analyzed. Adverse events were graded on the basis of National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 (*17*).

Table 1. Demographic Data of Osteosarcoma Patients

no.	sex	age (years)	weight (kg)	ECOG PS[a]	dose (g)
1	M	12	30	2	2
2	M	18	66	3	2
3	M	19	64	1	2
4	F	26	46	1	2
5	M	22	62	1	3
6	F	14	28	1	3
7	M	23	38	1	3
8	F	18	32	1	4
9	F	14	38	1	4
10	M	18	44	1	4
11	M	17	48	1	4

[a] Eastern Cooperative Oncology Group Performance Status.

Healthy Volunteers. Healthy human volunteers were selected following a rigid screening procedure for this single-dose, crossover, double-blind, comparative pharmacokinetic analysis of SLCP and 95% curcuminoids extract. This study was conducted in December 2007. The subjects included six men of Indian origin, in the age range of 18−40 years. Subjects with end organ damage or concurrent illness, those receiving concomitant medication, and tobacco or alcohol addicts were not included in the study. Volunteers were randomly assigned to the two groups. All subjects received both of the formulations at an interval of 2 weeks, allowing sufficient time for washout of the drug. The subjects were educated on food sources of curcumin and asked to avoid all "yellow" foods containing high concentrations of curcumin for 1 day before dose administration. A 1 day washout was selected due to the small amount of curcumin in curry-containing foods, the potential for noncompliance if a longer washout was instructed, and preliminary data showing no plasma curcumin in control subjects (data not shown). The subjects fasted for 10 h prior to dose administration and for 4 h after administration. SLCP and the 95% curcuminoids formula (containing >60% curcumin) were administered in capsule form at a single oral dose of 650 mg (containing 130−195 mg of curcumin from SLCP and >390 mg of curcumin from 95% curcuminoids extract), with 8 oz of water. The same dose quantity was selected to provide for adequate blinding, despite the difference in curcumin content. The dose was selected on the basis of preliminary animal and human pharmacokinetic data in healthy subjects (data not shown). Blood samples (5 mL) were collected in EDTA bulbs before dosing and at 1, 2, 3, 4, 6, and 8 h after administration. Eight hours was selected as the last time point in the healthy subjects group due to previous work showing curcumin excreted before this time (*11*, *13*). Subsequently, the final pharmacokinetic time point in osteosarcoma patients was extended to 12 h postdose. All procedures were performed in accordance with the institutional review board approved protocol. Plasma was separated from blood immediately and stored at −20 °C until analyzed.

Analysis of Curcumin in Dosage Form. The dosage form was analyzed using HPLC-PDA (Shimadzu 1100 series, India). The analytical column (Phenomenex, Luna C18 (2), 5 μm, 150 × 4.6) was used with mobile phase (MP) comprising MP-A, 0.1% phosphoric acid, and MP-B, acetonitrile, under gradient mode of separation with MP-A from 65 to 50 over the initial 20 min, with a flow rate of 1.5 mL/min and detector wavelength set at 425 nm.

Analysis of Plasma Curcumin. The identical HPLC-PDA system as noted in the curcumin dosage form analysis was used. The mobile phase was a mixture of 0.1% phosphoric acid (pH 5.1, adjusted with triethylamine)/acetonitrile (50:50 v/v). The injection volume was 20 μL, with a run time of 15 min, a flow rate of 1.5 mL/min, and the detector wavelength set at 425 nm. Autosampler carry-over was determined by first injecting the highest calibration standard before a blank sample. Negligible carry-over was observed, as indicated by the lack of curcuminoid peaks in the blank sample.

Sample Preparation. Plasma samples were prepared as follows: A 1.0 mL aliquot of each plasma sample was transferred to a screw-capped tube, and 3 mL of methanol was added. This mixture was vortexed for 1 min for protein precipitation to complete. The resulting solutions were incubated at 75 °C for 10 min, and the samples were again vortexed for 1 min followed by centrifugation at 5000 rpm for 3 min. The supernatant

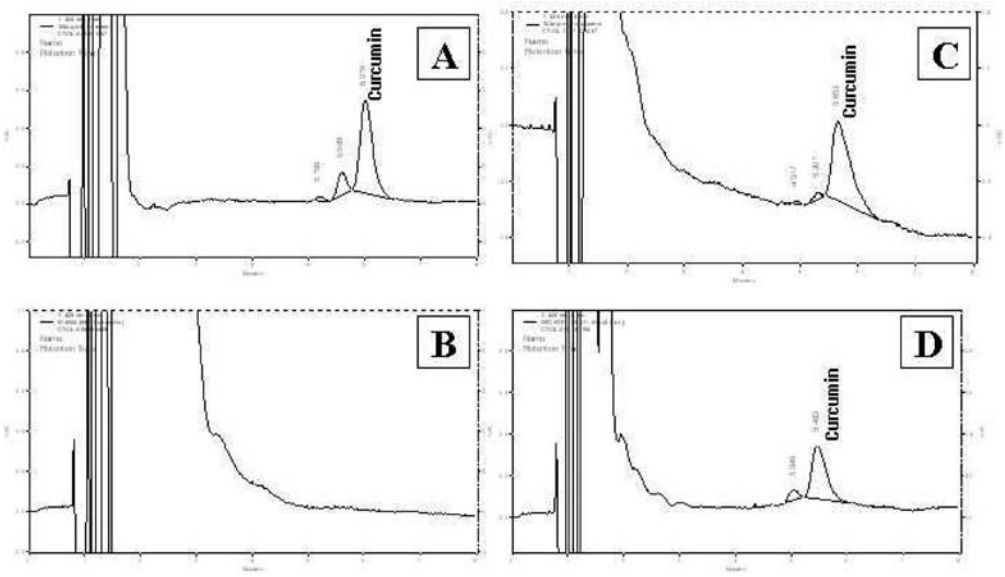

Figure 1. Representative HPLC chromatograms of (**A**) curcuminoids standard, (**B**) blank human plasma, (**C**) blank human plasma spiked with curcuminoids, and (**D**) human plasma of an osteosarcoma patient at 4.0 h after oral administration of SLCP.

was separated and filtered through a 0.2 μm membrane filter, and 100 μL of clear filtrate was injected into the HPLC system. No glucuronidase was used to prepare the samples.

Bioanalytical Method Validation. The method used for the analysis of curcumin from plasma was based on published methodology (*18*). The method was validated in our laboratory for limit of detection (LOD), lower limit of quantitation (LLOQ), linearity, and postextraction autosampler stability. The nine-point calibration curve was constructed by plotting peak area (y) of curcumin versus curcumin concentration (x). The regression parameters of slope, intercept, and correlation coefficient were calculated by linear regression using Microsoft Excel. To assess the intra- and interday precision and accuracy of the assay, linearity samples were prepared as described above. The intraday precision of the assay was assessed by calculating the relative standard deviation (RSD) for the analysis of linearity samples in three replicates, and interday precision was determined through the analysis of linearity samples on three consecutive days. Accuracy was determined by comparing the calculated concentration using calibration curves to the known concentration.

RESULTS

Under optimized HPLC-PDA conditions, curcumin was detected (**Figure 1A**). Because no late-eluting peaks were observed, regeneration of the column using a gradient elution step was not necessary. The total run time was 8 min, shorter than previously reported run times in the range of 15−40 min (*12*). Blank plasma showed no significant interfering peaks at the retention time (5.6 ± 0.5 min) of curcumin (**Figure 1B**). Panels **C** and **D** of **Figure 1** show the spiked plasma sample (100 ng/mL) and plasma of a patient at 4 h after drug administration, respectively.

The calibration curve was linear over the concentration range of 2−500 ng/mL of curcumin in human plasma, with correlation coefficient $r = 0.9989$. LOD and LLOQ were observed to be 1 and 2 ng/mL of curcumin in human plasma, respectively. No significant loss of curcumin was observed after storage of plasma at room temperature on the benchtop for 4 h. Processed samples were stable for 24 h in the autosampler tray.

Table 2 shows summary of intra- and interday precision and accuracy for curcumin in human plasma. The intraday accuracy of curcumin for human plasma samples was 96.4−102.1% at quality control (QC) samples with the precision (RSD) of <3.6%. The interday accuracy of curcumin for human plasma samples ranged from 95.4 to 101.3% at QC samples with the RSD of <4.8%.

Table 2. Precision and Accuracy of HPLC Analysis of Curcumin in Human Plasma[a]

nominal concentration (ng/mL)	measured mean ± SD	precision RSD%	accuracy DEV%
interday (n = 4)			
6	6.04 ± 0.11	1.86	0.67
250	224.81 ± 1.17	0.52	−10.08
400	282.46 ± 5.26	1.86	−29.39
intraday (n = 8)			
6	6.03 ± 0.11	1.87	0.51
250	216.79 ± 14.62	6.74	−13.29
400	291.18 ± 12.58	4.32	−27.20

[a] Accuracy defined as [(measured concentration − added concentration)/added concentration] × 100%). RSD%, relative standard deviation in percent; DEV%, percent deviation from nominal concentration.

Oral administration of SLCP or 95% curcuminoids extract in capsule form to healthy humans at a dose of 650 mg showed appreciable plasma concentrations from SLCP (**Figure 2**), compared to none detected for the 95% curcuminoids extract (**Table 3**). The AUC_{0-t} (ng min/mL) and AUC_{0-inf} (ng min/mL) of curcumin after oral administration with SLCP were 95.26 and 178.44, respectively (**Table 3**). These results show that the bioavailability of free curcumin was markedly improved after oral administration with SLCP. There were no adverse events reported by any participant.

SLCP administration to osteosarcoma patients via oral route in doses of 2000, 3000, and 4000 mg in capsule form showed high plasma concentrations and dose-related AUCs. The main pharmacokinetic parameters of the three doses in osteosarcoma patients are shown in **Table 4**. There were no adverse events reported after single oral administration of SLCP in healthy volunteers or in osteosarcoma patients.

DISCUSSION

The potential use of curcumin in cancer as primary care, chemotherapeutic adjuvant, and palliative care is of recent interest due to its multiple molecular targets, anti-inflammatory activity, and relatively good safety profile (*8*, *19*). Osteosarcoma is a malignant bone cancer with a poor prognosis, particularly after treatment options such as chemotherapy and surgery have

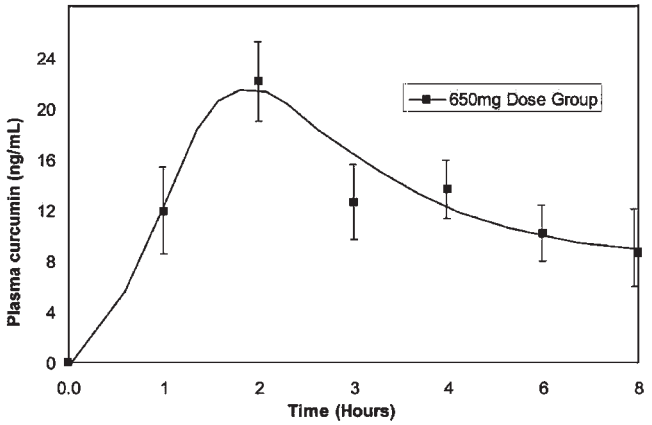

Figure 2. Mean free plasma curcumin concentration−time profiles of healthy human subjects (n = 6) after administration of 650 mg of SLCP. Analysis was performed by HPLC method as described. (All values expressed as mean ± standard error.)

Table 3. Pharmacokinetic Data from Healthy Human Subjects (n = 6) after Oral Administration of 650 mg of SLCP Formulation and 650 mg of 95% Curcuminoids[a]

parameter	650 mg SLCP dose	650 mg 95% curcuminoids dose
C_{max} (ng/mL)	22.43 ± 1.92	<1
t_{max} (h)	2.40 ± 0.44	NA
AUC $_{(0-t)}$ (ng/mL·h)	95.26 ± 4.62	NA
AUC $_{(0-inf)}$ (ng/mL·h)	178.44 ± 27.08	NA
$t_{1/2}$ (h)	7.46 ± 2.43	NA
K_{el} (per h)	0.10 ± 0.03	NA

[a] All values expressed as mean ±standard error. C_{max}, peak plasma concentration; t_{max}, time to peak concentration; AUC, area under the curve; $t_{1/2}$, half-life; K_{el}, elimination rate constant; NA, not applicable.

Table 4. Pharmacokinetic Data from Osteosarcoma Patients after Administration of 2000, 3000, and 4000 mg of SLCP Formulation[a]

parameter	2000 mg dose (n = 4)	3000 mg dose (n = 3)	4000 mg dose (n = 4)
C_{max} (ng/mL)	32.51 ± 3.88	31.42 ± 5.90	41.15 ± 8.94
t_{max} (h)	3.50 ± 0.37	1.50 ± 0.20	3.75 ± 1.61
AUC$_{(0-t)}$ (ng/mL·h)	153.96 ± 15.40	204.36 ± 52.27	270.76 ± 58.16
AUC$_{(0-inf)}$ (ng/mL·h)	189.26 ± 12.21	301.75 ± 41.69	375.25 ± 52.83
$t_{1/2}$ (h)	2.45 ± 0.47	7.50 ± 0.01	7.62 ± 1.09
K_{el} (per h)	0.28 ± 0.07	0.09 ± 0.002	0.09 ± 0.01

[a] All values expressed as mean ± standard error. C_{max}, peak plasma concentration; t_{max}, time to peak concentration; AUC, area under the curve; $t_{1/2}$, half-life; K_{el}, elimination rate constant.

been exhausted (*6*). There is a search for novel agents that may improve outcomes in osteosarcoma, and curcumin has been shown to inhibit the growth of osteosarcoma cells in vitro and reduce tumor volume and other cancer markers in vivo. Therefore, a clinical evaluation of prolonged dosage of SLCP for osteosarcoma is underway at Tata Memorial Centre, Mumbai, India. We report the findings of a substudy on the safety and pharmacokinetics of SLCP following a single oral dose. The findings of a similar study on healthy human volunteers using the same formulation are also discussed.

Recent attempts to increase the bioavailability of curcumin by dosing with glucuronidation inhibitors such as piperine (from *Piper niger*) have shown null results in clinical trials on cancer (*2*). This may be due to the potential of a zero-sum proposition achieved by inhibiting the body's endogenous detoxification system that permits increased levels of both nutrients and toxins. Recent approaches have attempted to increase curcumin's absorption by simple mixture with lipids or phospholipids. However, studies in several laboratories indicate only modest increases in bioavailability by simple mixing of curcumin with lipids or complexation with phospholipids (*20*−*22*).

Pharmacokinetic studies of curcumin demonstrate negligible free curcumin plasma levels even after high oral dosing. In a phase II study using unformulated curcumin, free curcumin was barely detectable in 19 patients who were administered 8 g of curcumin daily. However, a trend toward changes in blood markers was observed, suggesting that circulating plasma curcumin levels may not reflect tumor tissue curcumin levels (*11*). Several studies have reported that curcumin conjugates, such as the glucuronide, attain detectable levels in the plasma (*13*, *23*). However, the short half-life and low activity of the glucuronidated form compared to the free form may preclude its usefulness as a tool to understand curcumin's effects in translational (bench-to-bedside) research.

In healthy volunteers, the SLCP demonstrated increased bioavailability of curcumin as compared to an unformulated 95% curcuminoids extract. To what degree the enhanced bioavailability is a result of increased absorption or due to reduced conversion of free curcumin to conjugates is still not clear, because in this study the samples were not pretreated with glucuronidase. Several factors in the analysis of curcumin in biological fluids must also be explored, such as carry-over effects and degradation of curcumin between blood draw and analysis. Future studies at our center will focus on quantifying the metabolites of curcumin following oral administration of SLCP through validated methods.

Sustained levels of curcumin observed in our subjects and the nature of the SLCP suggest it continues to absorb into the bloodstream through the colon as it passes. Multiple mechanisms could be involved in higher exposure achieved with SLCP that need to be elucidated in future studies. The peak plasma concentration did not increase proportionately at the three dose levels of SLCP used in osteosarcoma patients. This might suggest a more complex absorption kinetics including a zero-order component or a difference in absorption between subjects who are healthy and those who have cancer. Prior pharmacokinetic studies were not able to detect any curcumin in plasma or serum past 8 h, so it was not deemed to be necessary to collect blood samples beyond 12 h after the dose. In both healthy volunteers and osteosarcoma patients, linear correlation between dose (measured as mg and mg/kg of body weight) and C_{max} or AUC was low ($R^2 < 0.1$, data not shown). The apparent correlation between dose and mean AUC in osteosarcoma patients (**Table 4**) was a result of one patient achieving very high AUC in 3 and 4 g cohorts, each influencing the mean. The limited number of subjects, combined with a relatively large interindividual variability in pharmacokinetics of polyphenols, warrants further study of SLCP in larger populations. In particular, the relationship of plasma and tissue levels of curcumin with biomarkers and clinical end points and the safety and tolerability after chronic dosing are areas of need for future study. To the best of our knowledge, this is the first report of a clinical trial of SLCP for any indication.

Our data suggest extended absorption parameters that could be specific to the formulation. SLCP is a proprietary formula; its activity is linked to key parameters such as curcumin/lipid/antioxidant ratio, globule-size distribution, and stability. In India, where curcumin- and lipid-rich curry is a staple of the diet, a lower incidence of Alzheimer's disease and many cancers is reported, leading some to believe there may exist a link. However, data from our laboratory and others show only slight (2−3-fold) increases in curcumin absorption by simply dissolving or mixing

curcumin in different types of lipids (data not included) (*20*−*22*). Yet formulations containing lipids and emulsifiers have shown positive effects in an in vivo colitis model (*24*). The magnitude of curcumin exposure achieved with SLCP and its commercial availability make it a viable candidate to explore effects of chronic low dosing for the prevention of disease.

In conclusion, our research has shown the relative bioavailability of curcumin administered as SLCP compared to generic curcumin extract in a single-dose pharmacokinetic study and suggests the potential for sustained release using lipid-based formulations such as SLCP. Furthermore, SLCP may be capable of achieving and maintaining plasma concentrations of curcumin above the threshold required for biological activity. However, further studies are warranted to evaluate the long-term tolerability after chronic dosing, as well as the relationship of plasma curcumin levels to biomarkers and clinical end points. The plasma concentration of curcumin achieved with 4 g of SLCP in the present study is in the same range shown to decrease disease markers such as isoprostanes, TNF-α, and amyloid β, primary markers linked to clinical end points for Alzheimer's disease and cancer. These results provide rationale to gather additional pharmacokinetic and clinical data using SLCP, and further work should be done to understand the dose−response and clinical impact of SLCP in larger sample sets and for various health issues where curcumin has shown promise in biological models.

ABBREVIATIONS USED

SLCP, solid lipid curcumin particle; NA, not applicable; C_{max}, maximum concentration; t_{max}, time to maximum concentration; AUC, area under the curve; $t_{1/2}$, half-life; K_{el}, elimination rate constant.

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