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ORIGINAL CONTRIBUTION

Increased bioavailability of curcumin using a novel dispersion technology system (LipiSperse®)

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Abstract

Purpose Curcumin has been shown to deliver protective effects against numerous degenerative conditions associated with high levels of inflammation and oxidative stress. Owing to its poor bioavailability when delivered orally, it is difficult to deliver a high concentration therapeutic dose. LipiSperse® is a novel delivery system that uses dispersion technology to enhance bioavailability of hydrophobic agents. In this study, we investigated the pharmacokinetics of a commercially available curcumin extract, with or without the curcumin-LipiSperse® delivery complex.

Methods Eighteen healthy male and female volunteers participated in this single equivalent dose, randomised, double-blinded study. Seven of those volunteers further participated in the crossover phase of the trial. Plasma concentrations were determined at baseline and at regular intervals over a 24-h period following 750 mg of curcuminoid ingestion.

Results In both the parallel and crossover trial, Curcumin with LipiSperse® delivered significantly higher plasma curcuminoid concentrations compared to the raw curcumin product (807 vs 318 ng/mL in the crossover trial).

Conclusions The novel delivery system LipiSperse® is safe in humans, and demonstrates superior bioavailability for the supply of curcumin when compared to a standard curcumin extract.

Keywords Curcumin · Curcuminoids · Pharmacokinetic · Bioavailability · LipiSperse®

Introduction

Beyond its principal role as a spice, the turmeric plant (*Curcuma Longa Li.*) has been used medicinally for nearly 4000 years in Indian, Chinese and Southeast Asian communities. Owing to this vast history of therapeutic use within eastern medicine, turmeric has become a target of heightened interest within evidence-based literature. In recent years, turmeric has been one of the most widely published integrative medicinal compounds with over 220 human clinical trials published on PubMed to date. Specifically, there is emerging data highlighting the adjuvant role of turmeric in the treatment of chronic conditions such as gastrointestinal upset, urinary tract infections and rheumatism [1].

In its dried and ground form, the turmeric rhizome contains 3–5% curcuminoids, which can be further divided into 75–80% diferuloylmethane (curcumin), 15–20% demethoxycurcumin (DMC) and 4–8% bis-demothoxycurcumin (BDMC) [2]. These derivatives all share the same chemical structure of two benzene methoxy rings joined by an unsaturated chain. Due to their β-diketone segments, curcuminoids undergo keto–enol tautomerisation (Fig. 1). In acidic and neutral solutions, curcuminoids exist predominantly in their keto form, whereas in alkaline solutions curcuminoids exist as stable enols. This enol arrangement gives curcuminoids the ability to chelate positively charged metals as well as donate and accept hydrogen bonds [3]. Further, the keto-enol tautomerisation allows the molecule to act as a Michael acceptor [4]. These collective properties provide curcuminoids with the capacity to exert anti-inflammatory, antioxidant and pro-apoptotic actions on numerous biological systems. Indeed, the consequences of such actions have gained considerable interest in the medical community.

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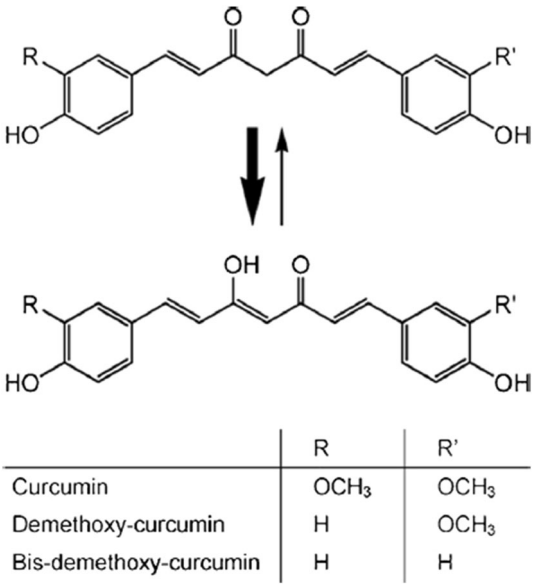

	R	R'
Curcumin	OCH_3	OCH_3
Demethoxy-curcumin	H	OCH_3
Bis-demethoxy-curcumin	H	H

Fig. 1 Chemical structure and tautomerisation of curcuminoids [5]

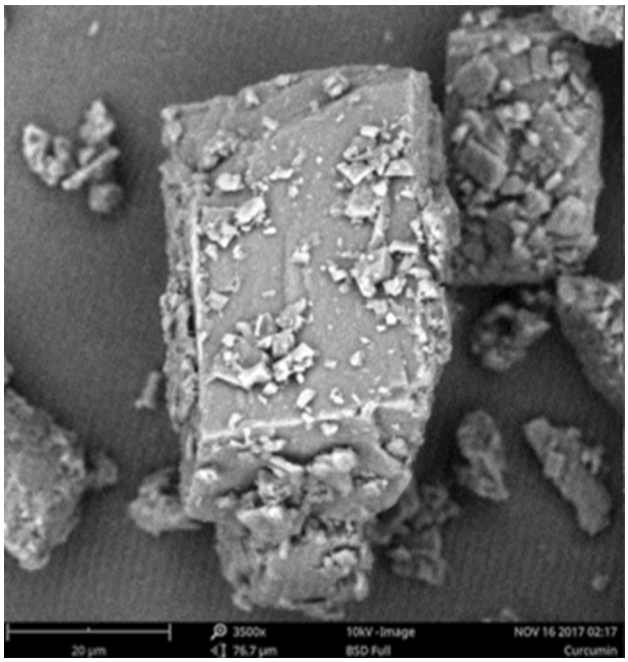

Fig. 2 Curcumin crystals viewed under scanning electron microscope (Phenom) at ×3500 magnification. Crystal structure is very chiselled and angular with a high degree of agglomeration with smaller particles and roughness. All of these factors decrease the crystal's ability to disperse in water

Curcumin has been shown to exhibit a protective effect against neurodegenerative [6, 7], cardiovascular [8, 9], endocrine [10, 11] and respiratory illnesses [12, 13]. A randomised controlled trial evaluating the effects of curcumin in adults with type 2 diabetes mellitus (T2DM) determined a 3-month treatment of 500 mg once-daily (OD) curcumin significantly ($p < 0.001$) improved markers of oxidative stress such as total antioxidant capacity and malondialdehyde compared to a placebo [10]. In adults with bronchial asthma, curcumin has been investigated as a therapeutic aid in parallel to conventional management. Following a 30-day exposure, participants treated with 500 mg bi-daily (BD) curcumin significantly improved their respiratory function reported as a reduction in airflow obstruction ($p < 0.001$) [12]. Unfortunately, the poor oral bioavailability of curcumin limits the extent to which these therapeutic outcomes can be further explored [2]. As such, much research has been devoted to understanding the pharmacokinetics of curcumin.

Low bioavailability of any pharmaceutical agent within the body is due to; (1) poor gastrointestinal absorption, (2) high rates of metabolism, (3) inactivity of metabolic products and, (4) rapid elimination and clearance [2]. Owing to its tautomeric structure, high-molecular weight and aromatic groups, curcumin is extremely hydrophobic, and therefore, only partially absorbed through the gastrointestinal epithelium [14]. One of the first studies to report this constraint identified virtually undetectable levels of plasma curcumin following a 1 g/kg oral dose in rats [15]. Once absorbed, curcumin is predominantly metabolised by the liver to form glucuronide and sulphate conjugates which represents ~99% of plasma curcumin [16]. These metabolites have largely been reported to have inferior bioactivity compared to free curcumin [17–19]. Lastly, the brief half-life of curcumin plays a crucial role in its low bioavailability. In rats, orally delivered curcuminoids are known to reach a peak plasma concentration at 0.83 ± 0.05 h, with an elimination half-life of 1.70 ± 0.58 h [20].

To overcome the pharmacokinetics which predispose poor bioavailability of orally ingested curcumin, several delivery techniques have been developed including adjuvants, nanoparticles, liposomes and self-nanoemulsifying drug delivery system (SNEDDS) [21]. The in vivo response to these have been varied [21], with several products posing a risk for drug–drug interactions due to their inhibition of the P-glycoprotein and CYP3A4 systems [22]. LipiSperse® is a novel delivery system tailored to increase the dispersion of crystalline lipophilic agents in aqueous environments. Lipophilic active ingredients provide challenges from a formulation and bioavailability perspective. Often, improving bioavailability leads to decreased active load in final formulations.

LipiSperse® is a mixture of surfactants, polar lipids and solvents specifically chosen for their ability to embed into the lipophilic crystal structure of the active ingredient, while keeping the hydrophilic head on the surface. This in turn increases the wettability of the crystal, by lowering the surface tension, which allows it to disperse in water (Figs. 2, 3). Once dispersed in water, LipiSperse® then goes on to

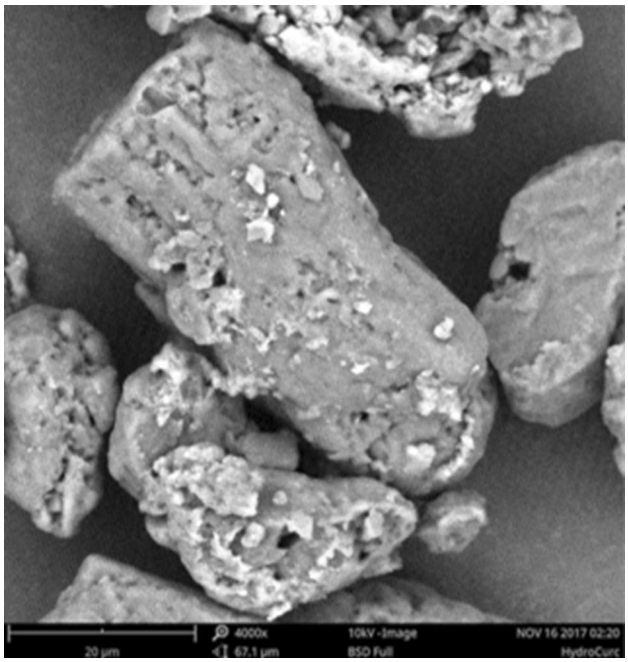

Fig. 3 Same curcumin crystals but now coated with LipiSperse®. Crystals are less angular and much smoother in appearance. The hydrophilic heads of the surfactant molecules are on the surface and ready to interact with water. In addition, less angles and less roughness decrease the contact angle with water, which increases dispersion in water

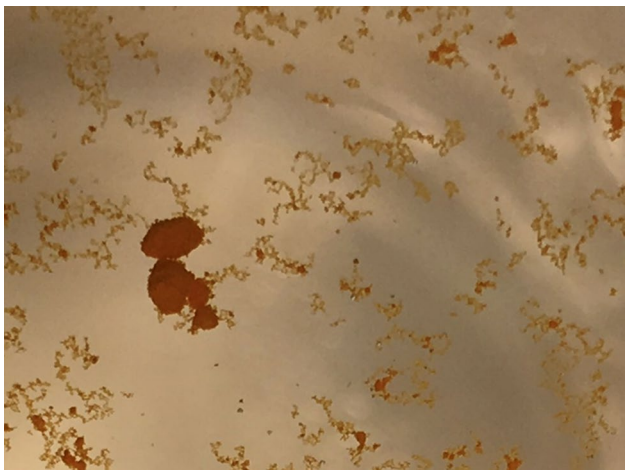

Fig. 4 Pure curcumin powder in water. Crystals are sticking together and agglomerating

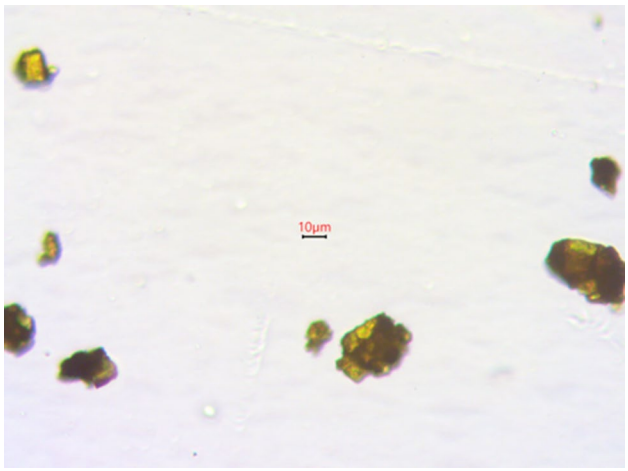

Fig. 5 Curcumin powder coated with LipiSperse® in water. Crystals are pushing each other apart—as seen under optical microscope (AmScope) at ×40

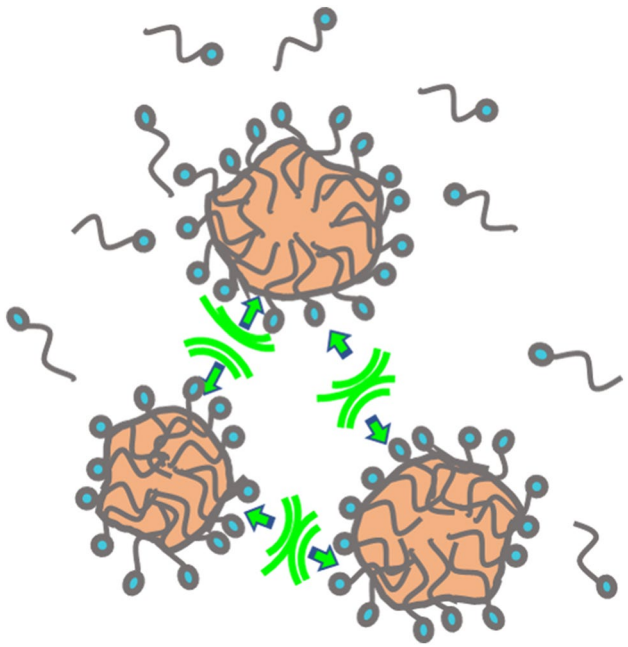

Fig. 6 Active crystals embedded with LipiSperse® in water. Repulsive forces between the particles prevent agglomeration or aggregation, allowing LipiSperse®-coated powders to have proper particle dispersion in water

prevent the crystals from agglomerating (Figs. 4, 5). Figure 6 is a graphical representation of the LipiSperse®-coated crystals dispersed in water.

LipiSperse® created cold-water-dispersible (CWD) powders are specifically designed to increase the bioavailability and functionality of lipophilic actives. CWD powders have an equilibrium established between the LipiSperse® on the powder surface and the LipiSperse® in the solution. Repulsive forces between the particles prevent agglomeration or aggregation: allowing CWD powders to have proper particle dispersion (Fig. 7).

The present study aimed to compare the pharmacokinetics of a single dose of commercially available curcumin with a curcumin-CWD LipiSperse® delivery complex.

Fig. 7 Standard curcumin (left) vs curcumin CWD Lipisperse® (right) delivery complex in cold water

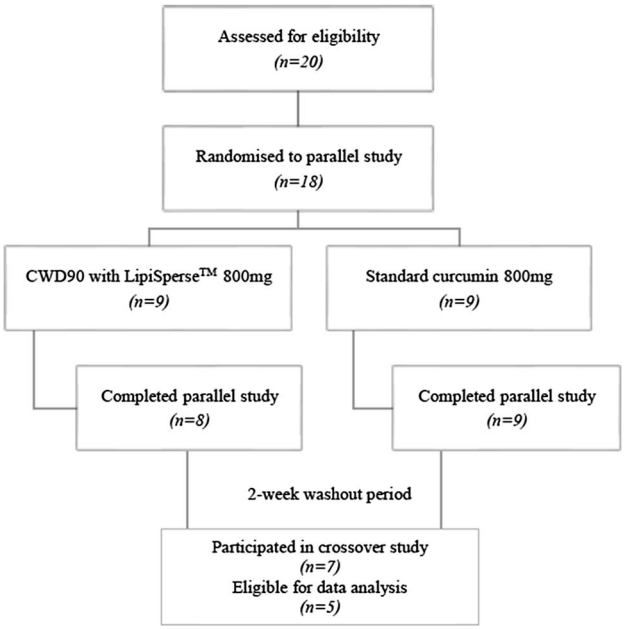

Fig. 8 Participant flow chart

Materials and methods

Design

A single equivalent dose, randomised, double-blinded parallel design with optional crossover was used to evaluate the pharmacokinetics of a commercially available curcumin product, with or without the curcumin-LipiSperse® delivery complex. This study was conducted in accordance with ethical approval from Bellberry Limited; an NHMRC accredited Human Research and Ethics Committee. All participants provided written informed consent and were screened for inclusion and exclusion criteria prior to commencing the study.

Participants

18 healthy volunteers (nine females, nine males) were recruited to take part in this study. Participants were excluded based on the presence of a clinically significant medical condition assessed at the time of recruitment. These included, but were not limited to; cardiovascular, neurological, psychiatric, renal, immunological, endocrine (including uncontrolled diabetes or thyroid disease) and haematological conditions. Other exclusion criteria included antioxidant supplementation (including curcumin products) within 3 months of testing, recent history (within 12 months) of substance abuse including alcohol, receiving treatment (radio and/or chemotherapy) for cancer (excluding squamous cell carcinoma or basal cell carcinoma skin cancer) in the past 2 years, known gastrointestinal or absorption issues, and development of adverse events/reactions in response to blood sampling which included, but were not limited to; fainting, life-threatening dehydration and/or serious bruising. Females who were pregnant or receiving fertility treatment were excluded from this study.

None of the participants in this trial were taking prescribed medications apart from the oral contraceptive pill. Participants were screened for known allergies/adverse reactions to the test product prior to dosing; none were reported.

Intervention

Following recruitment, participants were allocated into one of the two treatment groups using random allocation software (sealedenvelope.com). Upon completion of the parallel phase of the trial, participants were invited back to complete an optional crossover study following a 2-week washout period (Fig. 8). Upon returning for the crossover study, participants received the opposite trial product during the parallel study. Study preparations, experimental protocols and analysis methods were identical for both the parallel and crossover phase of the investigation. All subjects and investigators were blinded to the allocations during both trials until statistical analysis of all plasma samples had been completed.

Study preparations

The study arms were as follows: (1) Curcumin CWD 90 with LipiSperse® (Pharmako Biotechnologies, New South Wales) hard shell capsule (2 × 440 mg) containing 90% Curcuma longa extract and 10% LipiSperse® and (2) standard curcumin capsule (4 × 200 mg) containing 100% Curcuma longa extract. Curcuma longa extract contains 95% curcuminoids. Both products, therefore, provided a total dose of 750 mg of curcuminoids (80% curcumin, 17% DMC and 3% BDMC by weight). All preparations were given in non-descript capsules to ensure investigators and participants were blinded to the treatment arm until results were finalised. Prior to the study, capsules of each product were analysed for curcuminoid concentration (data not shown).

Protocol and blood sampling

Participants were required to complete an overnight fast (12-h) prior to the day of testing. Curcumin pharmacokinetics were determined from blood samples taken prior to dosing ($t = 0$), followed by intervals of 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6 and 24 h post supplementation. These time intervals were selected based on previous studies which show the majority of curcumin absorption to be completed within this period [21].

Samples were obtained from an antecubital vein using a 23 G Eclipse™ needle (BD, New Jersey) and 3 mL EDTA containing vacutainer (BD, New Jersey). Samples were then centrifuged at 4 °C for 10 min (2300 RPM). Once spun, plasma was separated and temporarily stored at − 20 °C (< 48 h) before being transported and stored at − 80 °C to await further analysis.

Participants were required to avoid foods containing curcumin, turmeric or curry powder from 24 h prior to testing until the collection of the final blood sample was complete. During the initial 6 h of testing, participants remained at the laboratory and were provided with standardized meals known to contain no trace of the test product. Participants were discharged between the 6- and 24-h sample; during this time, they were provided with a list of foods to avoid. Participants were monitored for adverse effects to the treatment during confinement and again when they returned for the 24-h sample.

Sample preparation

Standards

Curcumin was purchased from Sigma-Aldrich (08511-10MG) and stored at 2–8° as per manufacturer's instructions. The 1 mg standard was made up to 1 mL with ethanol for a concentration of 1 mg/mL. Working standard solutions were prepared by diluting the 1 mg/mL solution 1:10 using solution B mobile phase (details below). For this, 100 µL of the stock solution was added to 900 µL of mobile phase for a 0.1 mg/mL (100 µg/mL) solution. This solution was further diluted 1:10. For this, 100 µL was added to 900 µL of mobile phase for a 10 µg/mL solution. The 10 µg/mL solution constitutes our highest standard. Subsequent standard solutions were made by diluting the 10 µg/mL solution 1:10 with mobile phase for a 1 µg/mL solution, and then diluting the 1 µg/mL solution 1:10 with mobile phase for a 0.1 µg/mL solution and finally diluting the 0.1 µg/mL solution 1:0 with mobile phase for a 0.01 µg/mL solution. All solutions were prepared with the laboratory lights off and any blinds close to minimise light exposure. Once all standard solutions were made, they were temporarily stored at − 20° until ready for analysis. Fresh standards were made each day to prevent any potential degradation. The standard curve for each curcuminoid included a range that covered the biological sample values, with a lower limit of detection of 20 pg/mL.

Calculations

To accurately quantify the concentration of each of the curcuminoids, the 1 mg/mL solution was ran through the HPLC/MS-MS three times. After each pass, the ratio of each of the three curcuminoids (curcumin 78%, DMC 18% and DMC 4%) was established. From this ratio, the relevant concentrations could be adjusted for each of the curcuminoids for accurate quantification (e.g., the 1 mg/mL standard equated to 0.78 mg/mL of curcumin).

Internal standard/recovery

To account for the recovery of extracted samples, an internal standard (IS) of β-estradiol (Sigma-Aldrich—E8875-1G) was used. The addition of IS at the start of sample extraction allows us to trace the IS concentration through the assay and compare it with an aqueous standard solution with the same amount of IS added (considered 100%). The recovery percentage is then applied to the results to give an accurate concentration of curcumin in the sample. The concentration of IS added was 1 µg/mL made up of methanol. To calculate the recovery percentage of each sample, the following formula was used: [AUC (area under the curve) with extraction/AUC without extraction] × 100%.

Sample extraction

Plasma samples were extracted in accordance with previously published methods [21, 23, 24]. Briefly, plasma samples were removed from storage at − 80 °C and allowed to thaw at room temperature. Once thawed, 200 µL of sample or standard (1, 0.1, 0.01 µg/mL) was added to a microfuge

tube, along with 50 µL of internal standard in methanol and 20 µL of 3M HCl (to liberate free curcumin). This solution was briefly vortex mixed before being spiked with 100 µL of a solution containing 5 U/mL of type H-1 β-glucuronidase/sulfatase (G0751) from Helix pomatia (Sigma-Aldrich, Castle Hill, NSW) in 0.1 M phosphate buffer (pH 6.86). For enzymatic hydrolysation of the conjugates of curcumin, the resultant mixture was vortex mixed for 30 s and incubated at 37 °C for 1 h. During incubation, samples were constantly mixed. Following incubation, 1 mL of an extraction solution (95% ethyl acetate, 5% methanol) was added before samples were vortex mixed and sonicated for 15 min. The resulting solution was centrifuged at 13,000*g* for 10 min and the upper organic layer extracted to glass test tube and dried under nitrogen at 37 °C. Samples were reconstituted with 100 µl of methanol and transferred to a high performance liquid chromatography (HPLC) limited volume insert (200 µL capacity).

Chromatographic analysis

Chromatographic separation was carried out on an Agilent 1260 Infinity HPLC system using a Kinetex 5 µm C18, 250 × 4.6 mm with an AQ C18 4 × 3 mm SecurityGuard cartridge, all purchased from Phenomenex. The mobile phase consisted of solution A: distilled water with 0.1% formic acid, and solution B: 64% acetonitrile, 36% methanol and 0.1% formic acid run with a gradient with a flow rate of 1 mL/min. Starting with 40% solution B and increasing to 70% over the first 30 s. The solution B was increased to 80% at 7 min (1.5% per minute). This was increased to 95% at 8 min and held for 1 min before returning to 40% at 10 min. The column temperature was maintained at 30 °C and the analytes were quantified with an Agilent 6460 triple quad mass spectrometer with transitions as follows: Curcumin 369.2→285.2; demethoxycurcumin 338.9→255.0; bisdemethoxycurcumin 309.1→255.0.

Statistical analysis

Data were analysed using GraphPad Prism 7.0 (GraphPad Software Inc., California). The peak plasma concentration (C_{max}), time to maximum concentration (T_{max}), total area under the curve between $t = 0$ and $t = 6$ (Total AUC_{0-6h}), and relative area under the curve between $t = 0$ and $t = 6$ (Relative AUC_{0-6h}) were calculated for each subject. Mean, standard deviation (SD), and coefficient of variation (CV) of the above parameters were calculated for descriptive purposes. Data were assessed for normality using the Kolmogorov–Smirnov test. Inter-group differences in curcumin pharmacokinetics were evaluated using an analysis of variation (ANOVA). All tests were two tailed and an alpha level of 0.05 was applied as the criterion for statistical significance. Results are given as the mean ± SD unless otherwise stated.

Results

Of the eighteen volunteers recruited for this study, 17 (9 females and 8 males) completed the initial parallel phase of the trial. One participant withdrew following the first blood draw due to a sensation of dizziness. The average participant age was 25.6 years; all were within normal BMI range (20–25), non-smokers and otherwise healthy. Seven participants (5 males and 2 females) completed the crossover study following a 2-week washout period (Fig. 8). The average age of this subset of participants was 26.2 years. Data for two participants in the crossover group were removed due to insufficient plasma sample required for analysis. No adverse events were reported during the study.

No significant differences were reported in baseline curcumin, DMC or BDMC between either group both in the parallel and crossover trial ($p < 0.05$). Pharmacokinetic data of all curcuminoids measured during the crossover and parallel phase of the trial are reported in Tables 1 and 2, respectively. Baseline plasma concentrations for all curcuminoids were undetectable via HPLC, thus they have not been included in the tables.

In the crossover trial, C_{max} significantly increased in the CWD90 with LipiSperse® group as demonstrated by an 807 ng/mL increase in total plasma curcuminoids from baseline values ($p < 0.05$). Whilst the standard curcumin treatment also delivered a significant increase in total plasma curcuminoids from baseline ($p < 0.05$), the reported C_{max} for this group was significantly less than that of CWD90 with LipiSperse® ($p < 0.05$). Similar findings were seen in the parallel phase of the trial. Both treatment groups delivered significant increases in total plasma curcuminoids from baseline values ($p < 0.05$), however, C_{max} values for the CWD90 with LipiSperse® group were significantly greater than the standard curcumin group ($p < 0.05$) in both the crossover and parallel trial.

Over the initial 6 h, total AUC was significantly increased in the LipiSperse® group in both the crossover ($p < 0.05$; 1898 ± 270 vs 933 ± 260) and parallel trial ($p < 0.05$; 1773 ± 271 vs 756 ± 260). This effect was reduced when the data was extrapolated out to 24-h for both the crossover ($p = 0.14$; 2492 ± 392 vs 1907 ± 221) and parallel trial ($p = 0.10$; 2454 ± 617 vs 1878 ± 978).

Temporal data for of all curcuminoids measured during the crossover and parallel phase of the trial are reported in Figs. 9 and 10, respectively. For both formulations across each phase of the trial, total plasma curcuminoid concentrations peaked at 1 h following ingestion. All data returned to zero at the 24-h mark.

Table 1 Crossover pharmacokinetic parameters for curcumin, DMC, BDMC, and total curcuminoids after a single 750 mg dose of the two different curcumin preparations

	Group 1 CWD90 with LipiSperse® ($n=5$)				Group 2 Standard curcumin ($n=5$)			
	Curcumin	DMC	BDMC	Total	Curcumin	DMC	BDMC	Total
C_{max}	691 ± 124*	96.8 ± 27.3*	24 ± 11*	807 ± 155*	215 ± 224	22 ± 15	8 ± 5	318 ± 154
T_{max}	1	1	1	1	1	2	2	1
Total $AUC_{(0-6h)}$	1549 ± 206*	260 ± 51*	89 ± 13*	1898 ± 270*	787 ± 219	110 ± 31	36 ± 10	933 ± 260
Relative $AUC_{(0-6h)}$	258 ± 34*	43.8 ± 8*	15 ± 2*	316 ± 45*	131 ± 36	18 ± 5	6 ± 2	155 ± 43
Total $AUC_{(0-24h)}$	1998 ± 288	366 ± 77	128 ± 27	2492 ± 392	1621 ± 113	226 ± 87	60 ± 21	1907 ± 221
Relative $AUC_{(0-24h)}$	83 ± 12*	15 ± 3	5 ± 1	104 ± 16*	68 ± 5	9 ± 4	3 ± 1	79 ± 9

Values for C_{max} are reported in ng/mL. T_{max} is reported in hours. Total $AUC_{(0-6H)}$ is reported as ng/mL. Relative $AUC_{(0-6H)}$ is reported as ng/mL/h. Values reported as mean ± SD

*$p < 0.05$ compared to same measure in standard curcumin group

Table 2 Parallel pharmacokinetic parameters for curcumin, DMC, BDMC, and total curcuminoids after a single 750 mg dose of the two different curcumin preparations

	Group 1 CWD90 with LipiSperse™ ($n=8$)				Group 2 Standard curcumin ($n=9$)			
	Curcumin	DMC	BDMC	Total	Curcumin	DMC	BDMC	Total
C_{max}	658 ± 116*	97 ± 59*	26 ± 8*	781 ± 147*	151 ± 184	17 ± 15	7 ± 9	267 ± 153
T_{max}	1	1	1	1	1	3	2	1
Total $AUC_{(0-6h)}$	1438 ± 206*	253 ± 52*	82 ± 13*	1773 ± 271*	625 ± 219	99 ± 31	32 ± 10	756 ± 260
Relative $AUC_{(0-6h)}$	240 ± 34*	42 ± 9*	14 ± 2*	296 ± 45*	104 ± 37	17 ± 5	5 ± 2	126 ± 44
Total $AUC_{(0-24h)}$	1963 ± 436	364 ± 129	127 ± 52	2454 ± 617	1524 ± 832	280 ± 146	74 ± 27	1878 ± 978
Relative $AUC_{(0-24h)}$	82 ± 18	15 ± 5	5 ± 2	102 ± 25	63 ± 34	12 ± 6	3 ± 1	78 ± 41

Values for C_{max} are reported in ng/mL. T_{max} is reported in hours. Total $AUC_{(0-6H)}$ is reported as ng/mL. Relative $AUC_{(0-6H)}$ is reported as ng/mL/h. Values reported as mean ± SD

*$p < 0.05$ compared to same measure in standard curcumin group

Discussion

At present, there is a weight of evidence supporting the beneficial effects of curcuminoids for the treatment of conditions associated with excessive inflammation and oxidative stress [25]. However, curcumins traditionally poor oral bioavailability has limited its use. Numerous strategies have been developed to improve the bioavailability of this agent including cyclodextrin complexes [21], SNEDDS [22], nanoparticle colloidal dispersions [26] and nanoconjugates [27]. Given the variance in both the delivery technique and method used to quantify in vivo curcumin, it is difficult to compare many of the findings reported in the literature. As such, no strategy has emerged superior for the enhancement in bioavailability of orally delivered curcumin.

In the current study, we examined the effects of LipiSperse®, a novel delivery system that uses dispersion technology to enhance bioavailability of hydrophobic agents, on the bioavailability of a commercially available curcumin extract. Our trial was conducted under standardized conditions with the aim of controlling exogenous curcuminoids both prior to, and during the investigation. Consistent with similar research, baseline concentrations were essentially zero in both the test product and the standardized curcumin [21], thus we can confidently say there were no significance between group differences in plasma curcuminoids prior to dosage.

CWD 90 with LipiSperse® elicited the greatest increase in total plasma curcuminoid concentration, boasting a threefold improvement over the standard curcumin product. This outcome reflects the findings of prior investigations which support the superior bioavailability of curcumin delivery systems over raw curcumin products [21, 27, 28]. The rate-limiting factor for absorption of orally delivered drugs is a pre-epithelial aqueous barrier in the gastrointestinal lumen which impedes absorption of hydrophobic

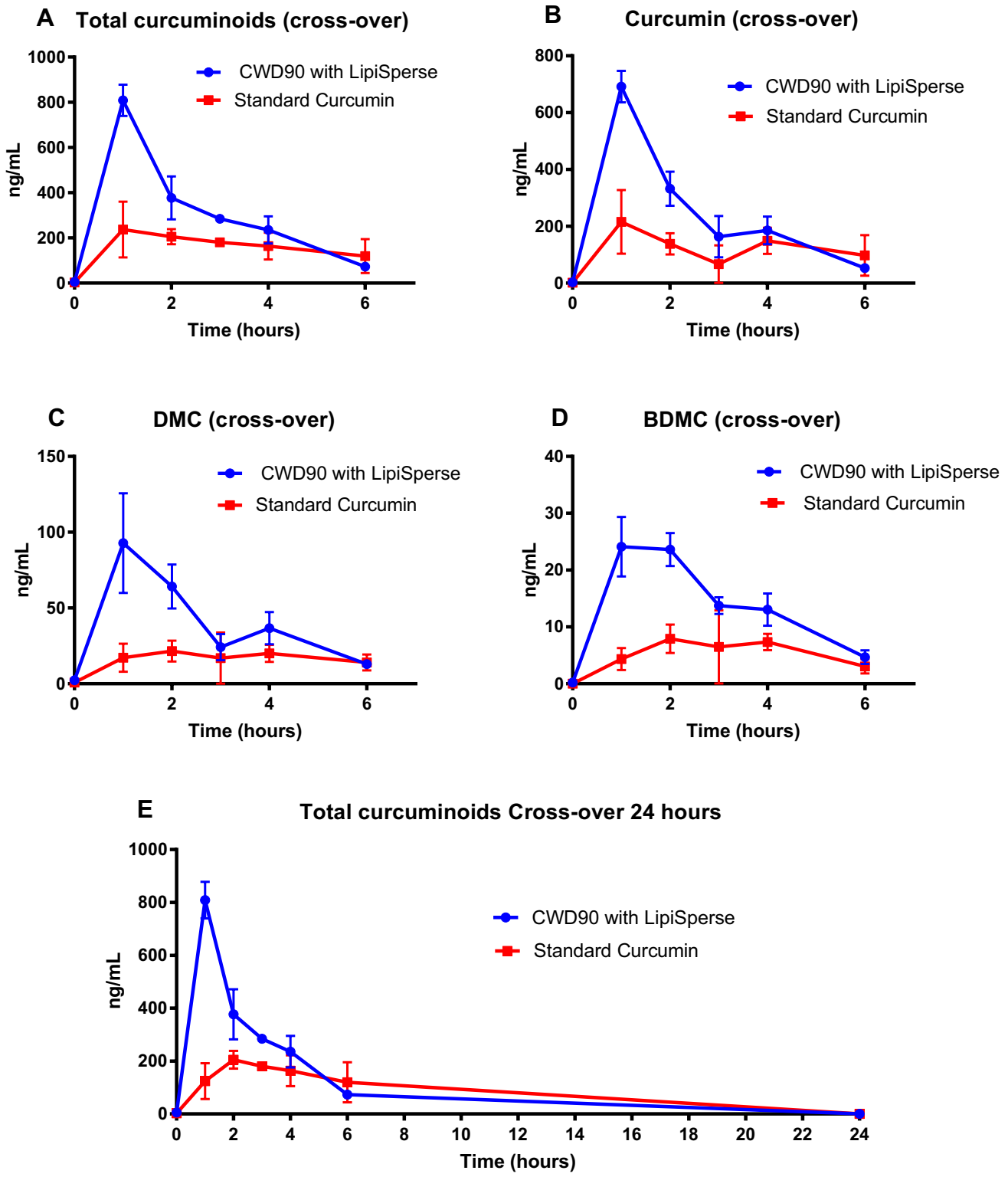

Fig. 9 Plasma concentration time curves during the crossover trial for total curcuminoids (top left), curcumin (top right), DMC (bottom left), and BDMC (bottom right) after a single 750 mg dose of the two different curcumin preparations. Concentrations are expressed in ng/mL. $n = 5$ per group

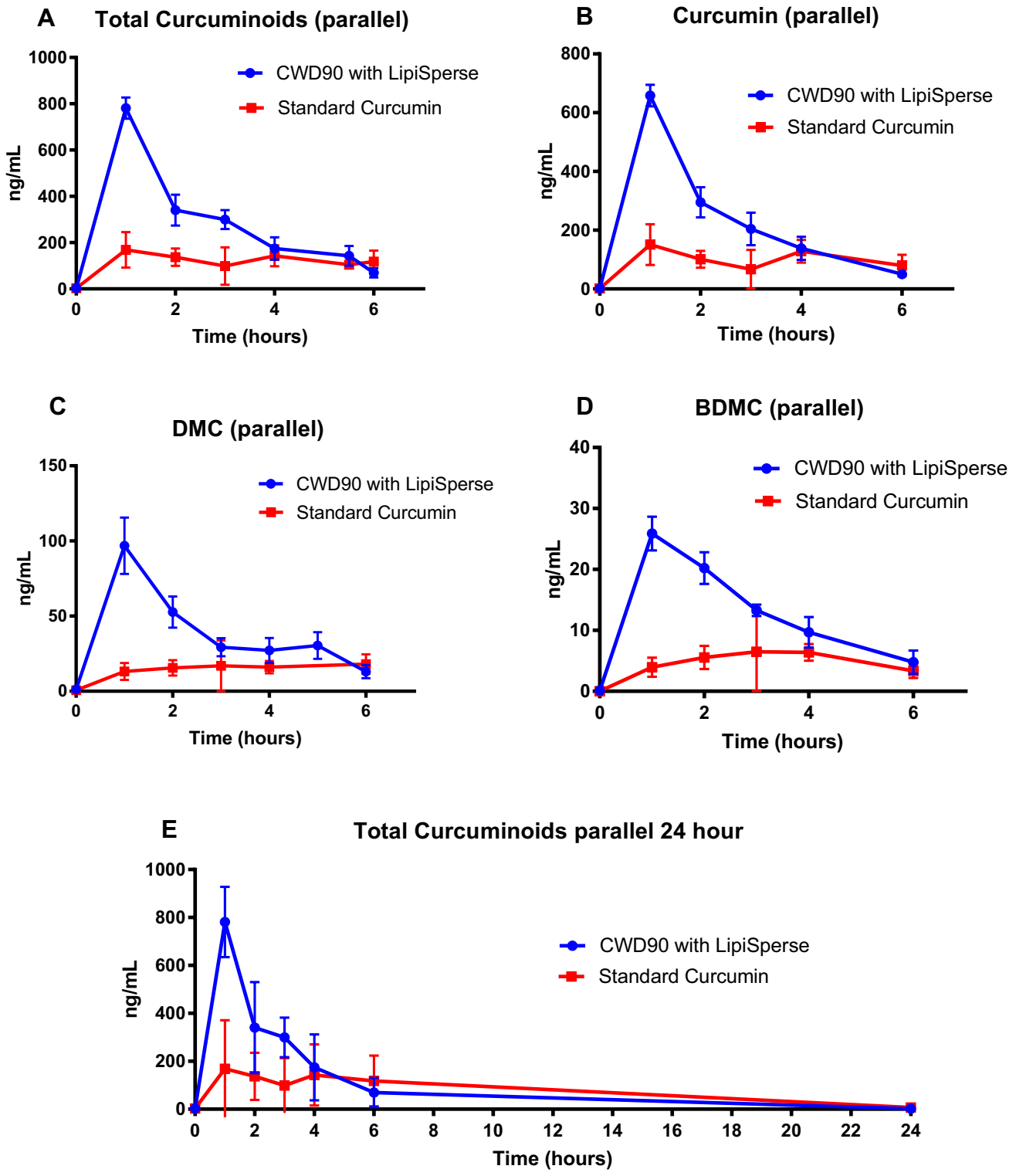

Fig. 10 Plasma concentration time curves during the parallel trial for total curcuminoids (top left), curcumin (top right), DMC (bottom left), and BDMC (bottom right) after a single 750 mg dose of the two different curcumin preparations. Concentrations are expressed in ng/mL. $n = 8$ (CWD90 with LipiSperse®), $n = 9$ (standard curcumin)

drugs [29]. By attaching itself to the surface of curcumin particles, LipiSperse® acts as a dispersing agent to lower the hydrophobicity of curcuminoids. Given this, the enhanced bioavailability reported for the test product in this study is likely due to increased gastrointestinal absorption secondary to a reduction in intermolecular forces.

Our trial demonstrated that 750 mg of curcuminoids combined with the LipiSperse® delivery system could increase plasma curcuminoid concentration by 807 ng/mL above baseline. Similar delivery techniques have been unable to match the efficacy of the dispersion system used in the present trial. Following the administration of 376 mg of curcumin paired with a novel cyclodextrin complex, Purpura et al. [21] reported a peak plasma curcuminoid concentration of 87 ng/mL. Given the pharmacokinetics of curcumin are non-linear [30], even with an equivalent dose this delivery system would fall considerably short of the plasma curcuminoid levels reported in our study. In this trial, baseline plasma curcuminoid concentration was negligible.

From a therapeutic perspective, the results of our study are promising. Following an 8-week exposure, 150 mg of curcumin per day has been associated with significant improvements in endothelial function as measured by flow-mediated dilation compared to matched controls [31]. This investigation used a previously validated curcumin product which had been found to deliver plasma C_{max} of approximately 150 ng/mL [26]. Indeed, this concentration is well below the 807 ng/mL reported for the LipiSperse® capsule, highlighting the potential role for the use of the LipiSperse® in future medical curcumin trials.

In this study, we successfully formulated an innovative preparation of curcumin with LipiSperse®. With an almost threefold increase in C_{max} and more than double the AUC after 6-h, LipiSperse® demonstrated it's oral bioavailability is superior to a standard curcumin formulation. However, one short fall of the study is the lack of data after 6 h. When the AUC data is extended to the 24-h data point, some of the AUC difference is negated. This is largely due to the apparent slower elimination rate of the standard formulation at 6 h. We speculate that if data was collected for 8–10 h, we may have seen a better representation of the pharmacokinetic profile of the two formulations. This is due to the 24-h time point having returned to baseline concentration. However, there is no way to know when in between the 6- and 24-h time points this occurred. Therefore, it is difficult to state the true AUC for the 24-h period. Due to this, we have chosen to focus on the 0–6-h data. Despite this limitation, the LipiSperse® formulation still has a greater, although not significant, AUC after 24 h compared to the standard formulation.

Of note, the oral bioavailability of curcuminoids has been shown to differ between sexes. In examining a liquid-micelle curcumin delivery system, the area under the plasma concentration–time curve was reported as twofold greater for women than for men [32]. This variance may be precipitated by the hepatic drug efflux transporter P-glycoprotein (responsible for curcuminoid metabolism), which is known to be more active in men. Further, smaller volumes of distribution due to differences in total body mass and blood volume may underpin the observed male–female discrepancies [33]. Analysis of our data showed there was no between-sex difference. This may be attributed to the sample size in our study. Indeed, the main difficulty with equating our trial to other investigations is that each study may have a different standard curcumin material, and each study has a different method of laboratory analysis. Therefore, each trial needs to be carefully considered on its own merits and the relative expression of data taken into consideration when making statements about the efficacy of a novel test product.

In conclusion, we examined the effect of a novel dispersion agent (LipiSperse®) on the pharmacokinetics of orally delivered curcumin via a single-dose bioequivalence study with crossover. Our findings suggest that when combined with LipiSperse®, plasma concentrations of curcumin can be significantly increased, providing further support for the use of delivery systems to improve bioavailability of poorly absorbed agents such as curcumin.

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Compliance with ethical standards

Conflict of interest No author listed on this manuscript has any conflict of interests to declare.

Ethical standards The manuscript was written through contributions from all authors who have given approval for the final version of the manuscript.

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