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RESEARCH ARTICLE

The oral bioavailability of curcumin from micronized powder and liquid micelles is significantly increased in healthy humans and differs between sexes

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Scope: Curcumin revealed various health-beneficial properties in numerous studies. However its bioavailability is low due to its limited intestinal uptake and rapid metabolism. The aim of our project was to develop novel curcumin formulations with improved oral bioavailability and to study their safety as well as potential sex-differences.

Methods and results: In this crossover study, healthy subjects (13 women, 10 men) took, in random order, a single oral dose of 500 mg curcuminoids as native powder, micronized powder, or liquid micelles. Blood and urine samples were collected for 24 h and total curcuminoids and safety parameters were quantified. Based on the area under the plasma concentration–time curve (AUC), the micronized curcumin was 14-, 5-, and 9-fold and micellar curcumin 277-, 114-, and 185-fold better bioavailable than native curcumin in women, men, and all subjects, respectively. Thus, women absorbed curcumin more efficiently than men. All safety parameters remained within the reference ranges following the consumption of all formulations.

Conclusion: Both, the micronized powder and in particular the liquid micellar formulation of curcumin significantly improved its oral bioavailability without altering safety parameters and may thus be ideally suited to deliver curcumin in human intervention trials. The observed sex differences in curcumin absorption warrant further investigation.

Keywords:
Bioavailability / *Curcuma longa* / Curcumin / Healthy humans / Safety / Sex differences

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1 Introduction

Curcumin is a lipophilic phenolic substance with a characteristic yellow color derived from the rhizome of the plant turmeric (*Curcuma longa*) and is commonly used as an additive (E100) for food coloring and flavoring by the food industry and in private homes, especially in the Indian subcontinent [1]. Curcumin is the most biologically active constituent of the curry spice turmeric and possesses a number of beneficial biological and pharmacological activities [2]. Curcumin was suggested to act on multiple molecular and cellular targets in the pathophysiology of cancer [3,4], diabetes mellitus [5], cardiovascular [6–9], neurological diseases [10], multiple sclerosis [11], and rheumatism [12]. The mechanisms implicated include anti-inflammatory [13–15], antioxidant [16], immunemodulatory [17], proapoptotic [18–20], and antiangiogenic activities [21–23], and the prevention of mitochondrial dysfunction [24, 25].

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Abbreviations: AUC, area under the plasma concentration–time curve; **BDMC**, bis-demethoxycurcumin; C_{max}, maximum plasma concentration; **DMC**, demethoxycurcumin; T_{max}, time to reach the maximum plasma concentration

The trial was registered at clinicaltrials.gov with the study ID NCT01925287.

Although these data indicate beneficial effects of curcumin in the context of various diseases, its low systemic bioavailability hinders its clinical development [26]. Curcumin is biotransformed, predominantly in the liver, to dihydrocurcumin and tetrahydrocurcumin and these metabolites are converted to mono-glucuronidated conjugates. Curcumin-, dihydrocurcumin-, and tetrahydrocurcumin-glucuronides, as well as tetrahydrocurcumin are the major metabolites of curcumin in vivo [27]. In humans, due to its fast metabolic turnover in the liver and intestinal wall, blood concentrations of curcumin are low and tissue distribution is limited following oral dosing [28–36]. Maximum plasma curcumin concentrations in humans, even upon intake of doses as high as 10 or 12 g curcumin, remain in the low nanomolar range (<160 nmol/L) [30].

In consideration of the potent health-beneficial properties of curcumin, researchers have tried to increase the uptake and retention of the phytochemical in the body. A number of different strategies, such as the inhibition of curcumin metabolism with adjuvants and novel solid and liquid oral delivery systems, have been investigated for their potential to enhance the biological availability of curcumin [28, 37–41]. Pharmacokinetic data for novel oral delivery systems, namely the concomitant administration of the adjuvant piperine with curcumin and the application of crystalline curcumin in a micronized form, have been published recently and suggest an ~20- and ~28-fold increase in bioavailability (based on area under the plasma concentration–time curve (AUC)) compared to native curcumin, respectively [28, 39].

As the extent to which a substance can be absorbed depends on its solubility in the aqueous phase of the digestive fluids, we aimed at testing two different strategies, namely micellation and micronization, to enhance the aqueous solubility of curcumin. Both micronization and micellar formulation are common methods employed to enhance the bioavailability of drugs [42]. Curcumin was thus incorporated into a micronized powder or liquid micelles and its absorption and excretion kinetics were investigated in a single-blind crossover study with healthy female and male subjects. A particular aim of our project was to investigate potential sex differences in curcumin absorption and the safety of the novel curcumin formulations in healthy humans.

2 Subjects and methods

2.1 Curcumin formulations

The native curcumin powder (Jupiter Leys, Cochin, Kerala State, India) used in all formulations contained 82% curcumin, 16% demethoxycurcumin (DMC), and 2% bisdemethoxycurcumin (BDMC). The curcumin micronisate was produced by RAPS GmbH & Co. KG (Kulmbach, Germany) using their "concentrated powder form" technology [43] by mixing 25% curcumin powder with 58.3% triacetin and 16.7% panodan (E472e) and spraying the solution onto the porous excipient silicon dioxide. The resulting curcumin micronisate contained 17.2% curcumin powder, which is equivalent to 14.1% curcumin. Curcumin micelles were composed of 7% curcumin powder (equivalent to 6% curcumin) and 93% Tween-80 (Kolb, Hedingen, Switzerland) and manufactured by AQUANOVA AG (Darmstadt, Germany). All percentages refer to weight.

2.2 Subjects

Twenty-three healthy subjects (13 women, 19–28 years; 10 men, 20–28 years) with routine blood chemistry values within the normal ranges participated in this study (Table 1). Exclusion criteria were overweight (BMI >30 kg/m^2), metabolic and endocrine diseases, pregnancy, lactation, drug abuse, use of dietary supplements or any form of medication (with the exception of oral contraceptives), smoking, frequent alcohol consumption (>20 g ethanol/day), adherence to a restrictive dietary regimen, physical activity of more than 5 h/wk, participation in a clinical trial within the past 3 months prior to recruitment, or a known intolerance against curcuma. All subjects were asked to maintain their regular lifestyles and usual extent of physical activities during the study period. The study protocol was approved by the ethics committee of the State Medical Society of Baden-Württemberg, Germany, and was in conformance with the Declaration of Helsinki. Written informed consent was obtained from all participants before inclusion in the trial.

2.3 Study design

2.3.1 Run-in phase

The volunteers were asked to avoid foods containing curcumin, turmeric (*C. longa Linn.*), or curry for 1 wk prior to and throughout the entire study. To this end, a list of foods containing curcumin (E100) was provided. Compliance with these dietary restrictions was controlled by measuring concentrations of curcumin, DMC, and BDMC in fasting plasma samples and urine samples at baseline.

2.3.2 Intervention

The study followed a single-blind crossover design with three study arms separated by ≥1-wk washout periods. A standardized dinner was provided on the evening before the trial and standardized meals were provided during the entire day of the intervention (see Supporting Information Table 1). The curcumin formulations were administered in the morning after a 12 h overnight fast. All participants orally ingested in random order a single dose of 500 mg curcuminoids (containing 410 mg curcumin, 80 mg DMC, and 10 mg BDMC) as native powder, micronized powder, or liquid micelles mixed

Table 1. Baseline characteristics (mean ± SD) of the participants at screening[a)]

Variable	Women ($n = 13$)	Men ($n = 10$)	p-Value
Age (years)	23 ± 3	25 ± 3	ns
Body height (m)	1.65 ± 0.06	1.76 ± 0.06	0.0019
Body weight (kg)	57.1 ± 3.1	73.6 ± 11.1	0.0011
BMI (kg/m^2)	21.1 ± 1.5	23.8 ± 2.6	0.0201
Total cholesterol (mg/dL)	184 ± 21.3	178 ± 37.0	ns
LDL cholesterol (mg/dL)	112 ± 20.3	110 ± 30.6	ns
HDL cholesterol (mg/dL)	67 ± 14.4	52 ± 9.6	0.0086
Triacylglycerols (mg/dL)	95 ± 43.9	97 ± 47.3	ns
Fasting plasma glucose (mg/dL)	82 ± 11.4	86 ± 10.6	ns
Haematocrit (%)	43.5 ± 2.4	46.4 ± 2.2	ns
Blood Hb (g/dL)	14 ± 0.2	16 ± 0.7	0.0119
Systolic blood pressure (mmHg)	124 ± 11.2	131 ± 13.3	ns
Diastolic blood pressure (mmHg)	75 ± 6.8	73 ± 3.4	ns

a) Statistical differences between women and men were calculated by an unpaired Student's t-test.

into 50 g woodruff syrup. Water was available for consumption during the entire day and neither food nor water intake were restricted during meals. Blood samples were collected at: 0 (before curcumin ingestion), 0.5, 1, 1.5, 2, 4, 6, 8, and 24 h after the curcumin dose. Blood samples were drawn from an indwelling venous cannula. Urine was collected starting with the second voiding of the bladder during the 24-h period of the intervention day. Urine bottles (containing 30 mL of a 10% phosphoric acid solution) were exchanged just before (0), and then at 6, 12, and 24 h after curcumin intake. Urine volumes were recorded and 15 mL aliquots for each period were stored at −80°C until analyzed.

2.3.3 Blood sampling and processing

For the determination of plasma concentrations of curcumin, BDMC, and DMC, blood was collected in tubes containing EDTA (Sarstedt AG & Co, Nümbrecht, Germany), immediately centrifuged (1008 × *g*, 10 min, 4°C), and the obtained plasma samples were stored at −80°C until further analysis. For the analyses of total, LDL-, and HDL-cholesterol, triacylglycerols (TAG), and liver and kidney function markers (all analyses performed by the clinical laboratory Laborärzte Sindelfingen, Sindelfingen, Germany), and serum was obtained from blood sampled at the 0, 4, and 24 h time points.

2.4 HPLC analyses of curcumin, DMC, and BDMC in plasma and urine samples

Curcuminoids were extracted using a modified method of Heath et al. [44]. Plasma and urine samples were thawed in the dark at room temperature. One milliliter plasma and 10 μL 10 N hydrochloric acid were pipetted into a test tube. Urine samples were adjusted to pH 4.5–5.0 with sodium hydroxide or hydrochloric acid, respectively, and 1 mL transferred into a test tube. To each plasma or urine sample, 100 μL beta-glucuronidase type H-1 from Helix pomatia (3 mg/100 μL in 0.1 M sodium acetate buffer; Sigma-Aldrich Chemie GmbH, Schnelldorf, Germany) were added and samples incubated at 37°C for 45 min. Plasma samples were extracted with 3 mL of extraction solvent (95% ethyl acetate and 5% methanol v/v) and inverted for 30 min. Urine samples were extracted with 3 mL of extraction solvent and vortex-mixed for 30 s. Samples were centrifuged at 1008 × *g* for 5 min at 4°C and the supernatants transferred to clean glass tubes. The extraction was repeated twice with 3 mL extraction reagent and the pooled supernatants were evaporated to dryness using an RVC 2–25 CDplus centrifugal evaporator (Martin Christ Gefriertrocknungsanlagen GmbH, Osterode am Harz, Germany). The dried residue was dissolved in 150 μL methanol, vortex-mixed for 30 s, left in the dark at room temperature for at least 10 min, and vortex-mixed again (20 s). The content of each test tube was transferred to an HPLC sample vial and 20 μL injected into the HPLC system. Chromatographic separation was carried out on a Jasco X-LC system (3180MX, 3159AS, 3185PU; Gross Umstadt, Germany) using a Kinetex PFP column (150 × 4.6 mm, 2.6 μm; Phenomenex, Aschaffenburg, Germany) and a mobile phase of 3.25% ACN, 61.75% methanol, and 35% deionized water (all by vol; adjusted to pH 3 with perchloric acid), which was delivered at a flow rate of 1.6 mL/min. The column temperature was maintained at 30°C and the analytes were quantified with a Jasco X-LC 3120FP Fluorescence Detector with excitation and emission wavelengths set at 426 and 536 nm. Curcuminoids were quantified against external standard curves. Curcumin (CAS # 458–37–7; purity ≥97.2%), DMC (CAS #22608-11-13; purity ≥98.3%), and BDMC (CAS # 24939-16-0; purity ≥99.4%) standards were obtained from Chromadex (Irvine, USA).

2.5 Statistical analyses

Statistical analyses were performed and the AUC was calculated using the software package GraphPad Prism 6

Table 2. Pharmacokinetic variables (mean ± SD) calculated from plasma total curcumin, DMC, and BDMC concentrations in healthy human subjects after a single oral dose of 500 mg curcuminoids (410 mg curcumin, 80 mg DMC, and 10 mg BDMC) as native powder, micronized powder, or liquid micelles[a)]

	Curcumin			DMC			BDMC		
	Women	Men	All	Women	Men	All	Women	Men	All
AUC[b),c)] (nmol/L · h)									
Native	50.8 ± 50.8	84.8 ± 168.9	65.6 ± 115.6	10.1 ± 10.0	7.0 ± 5.4	8.7 ± 8.3	3.22 ± 2.66	3.1 ± 2.0	3.2 ± 2.4
Micronisate	699.9 ± 288.2	413.4 ± 199.3	582.7 ± 288.8	296.1 ± 115.7	174.9 ± 86.5	246.5 ± 119.3	32.95 ± 13.90	18.5 ± 5.4	27.4 ± 13.3
Micelles	14074.6 ± 4571.3	9642.7 ± 3217.6	12147.7 ± 4547.5	1479.3 ± 500.7	891.7 ± 279.3	1223.8 ± 507.3	43.92 ± 16.94	27.7 ± 9.0	37.3 ± 16.2
p For formulation	<0.0001			<0.0001			<0.0001		
p For sex	0.0090			0.0003			0.0336		
p For formulation × sex	0.0034			0.0006			ns		
C_{max} (nmol/L)									
Native	4.6 ± 3.3	10.4 ± 19.7	7.1 ± 13.2	1.3 ± 0.9	2.0 ± 1.0	1.5 ± 1.0	0.43 ± 0.19	0.7 ± 0.4	0.5 ± 0.3
Micronisate	50.6 ± 26.4	28.4 ± 12.9	41.6 ± 24.3	38.7 ± 17.3	27.7 ± 13.1	34.5 ± 16.4	5.46 ± 2.10	4.6 ± 2.7	5.1 ± 2.3
Micelles	3701.4 ± 1425.5	2612.5 ± 1180.4	3228.0 ± 1408.2	495.6 ± 195.0	358.8 ± 140.6	439.6 ± 184.3	11.43 ± 6.23	8.9 ± 4.4	10.4 ± 5.6
p For formulation	< 0.0001			<0.0001			<0.0001		
p For sex	ns			ns			ns		
p For formulation × sex	0.0314			ns			ns		
T_{max} (h)									
Native	7.6 ± 7.9	7.5 ± 9.0	7.5 ± 8.2	3.9 ± 3.4	3.8 ± 2.9	3.8 ± 3.1	2.0 ± 1.0	2.0 ± 1.1	2.0 ± 1.0
Micronisate	7.7 ± 5.0	10.4 ± 8.1	8.8 ± 6.4	1.4 ± 0.5	1.1 ± 0.4	1.3 ± 0.5	1.5 ± 0.5	1.1 ± 0.4	1.3 ± 0.5
Micelles	1.1 ± 0.4	1.2 ± 0.4	1.1 ± 0.4	0.9 ± 0.4	1.1 ± 0.4	1.0 ± 0.4	1.2 ± 0.5	1.3 ± 0.3	1.2 ± 0.4
p For formulation	0.0001			<0.0001			0.0025		
p For sex	ns			ns			ns		
p For formulation × sex	ns			ns			ns		

a) Two-way ANOVA was performed using the software package GraphPad Prism 6 for Mac OS X (version 6.0b; GraphPad Software, Inc.) to evaluate effects attributed to curcumin formulation and to sex. The number of observations (*n*) was 13 women and 10 men for the native curcumin and curcumin micelles, and, because of a dropout during the study, nine men for the curcumin micronisate intervention.
b) AUC, area under the plasma concentration time curve; C_{max}, maximum plasma concentration; T_{max}, time to reach C_{max}.
c) AUC was computed using the software package GraphPad Prism 6 for Mac OS X (version 6.0b; GraphPad Software, Inc.).

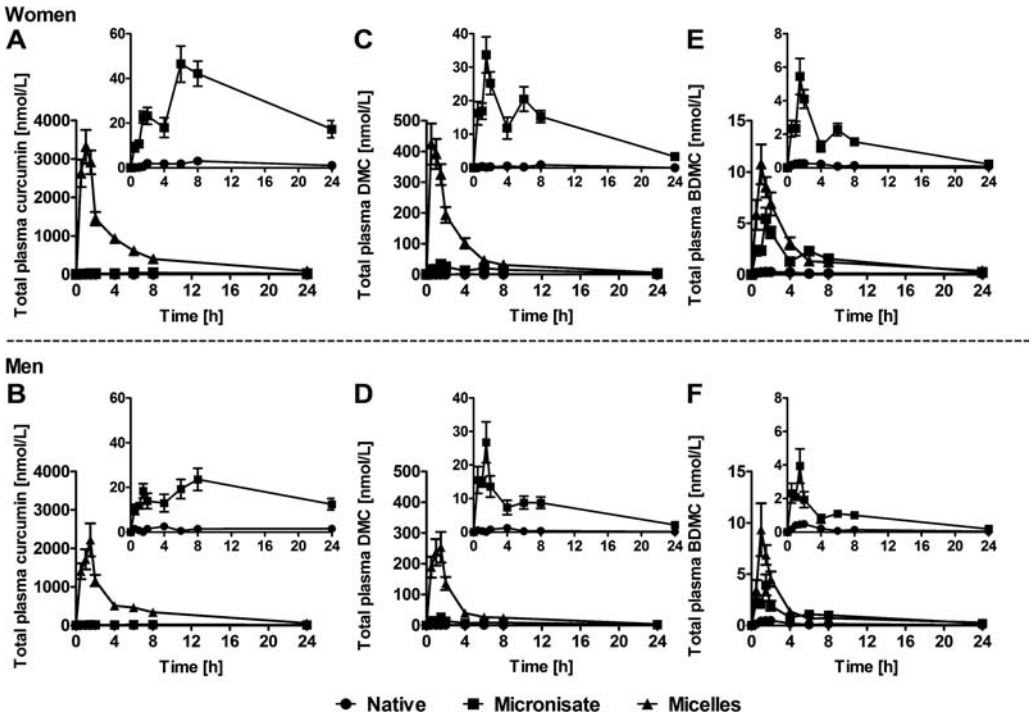

Figure 1. Mean (± SEM) total plasma curcumin (A, B), DMC (C, D), and BDMC (E, F) concentrations (nmol/L) following the ingestion of a single oral dose of 500 mg curcuminoids (410 mg curcumin, 80 mg DMC, 10 mg BDMC) as native (dots), micronisate (squares), or micelles (triangles) in women ($n = 13$) and men ($n = 10$). The small inserts show the comparisons between native and micronized curcumin only.

for Mac OS X (version 6.0c; GraphPad Software, Inc., La Jolla, CA, USA). Differences between baseline characteristics (Table 1) in women and men were calculated by an unpaired Student's *t*-test. The effects of the different curcumin formulations and sex on absorption kinetics (Table 2) were analyzed by a two-way ANOVA. Differences between baseline (0 h) and the following time points among the three treatment groups were tested for significance by repeated measures ANOVA. Differences were considered significant at $p < 0.05$. Reported values are arithmetic means with SD or SEM, as indicated.

3 Results

3.1 Baseline characteristics of the participants, safety parameters, and adverse effects

Routine blood chemistry values were within the normal ranges for all subjects at baseline (Table 1). Mean systolic blood pressure in males was slightly higher than the normal range, but was accepted because it is unlikely to affect absorption and excretion kinetics. All participants were within the normal range for BMI and blood lipids. Men, compared with women, had a significantly higher BMI, lower fasting serum HDL cholesterol concentrations as well as higher blood hemoglobin concentrations at the time of screening (Table 1). Serum lipids and biomarkers of liver and kidney function were all within normal ranges at baseline as well as 4 and 24 h after the administration of the different curcumin formulations and no significant differences were observed between groups (Supporting Information Table 2). The following adverse effects were reported after the intake of native curcumin: flatulence (one man), stomach ache (one man), and yellowish stool (one man); of micronized curcumin: yellowish diarrhea (one woman), yellowish stool (one man and one woman), and an increase of the stool volume (one woman); and of curcumin micelles: mild nausea (seven women, three men), vomiting (one woman), mild fatigue (one woman), mild headache (one woman), mild stomachache (one woman), and incidental regurgitation (one woman).

3.2 Plasma total curcumin, DMC, and BDMC

Curcumin, DMC, or BDMC were not detected in any of the baseline fasting plasma samples. Maximum plasma total curcumin, DMC, and BDMC concentrations (maximum plasma concentration (C_{max})) and their respective AUC were significantly higher after the consumption of curcumin micronisate and micelles than native curcumin (Fig. 1). A significant gender effect was observed for AUC; women had significantly higher plasma AUC than men for all three curcuminoids, with the only exception of total plasma curcumin AUC for native curcumin, which was numerically higher due to the

Table 3. Cumulative urinary excretion of curcumin, DMC, and BDMC (nmol/g creatinine; mean ± SD) over 24 h in subjects consuming a single oral dose of 500 mg curcuminoids (410 mg curcumin, 80 mg DMC, and 10 mg BDMC) as native powder, micronized powder, or liquid micelles[a)]

	Curcumin			DMC			BDMC		
	Women	Men	All	Women	Men	All	Women	Men	All
Native	7.0 ± 4.9	4.0 ± 2.6	5.1 ± 3.3	6.1 ± 7.1	2.5 ± 3.2	3.5 ± 3.4	1.0 ± 0.9	0.4 ± 0.2	0.6 ± 0.6
Micronisate	95.4 ± 57.1	33.4 ± 15.8	70.6 ± 54.3	67.3 ± 58.6	20.5 ± 12.7	51.4 ± 54.0	5.8 ± 2.6	2.0 ± 0.6	4.2 ± 2.6
Micelles	961.5 ± 267.8	503.7 ± 223.0	753.4 ± 336.6	301.1 ± 68.5	122.9 ± 62.4	217.8 ± 113.4	9.0 ± 4.0	4.8 ± 1.9	7.1 ± 3.8
p For formulation	<0.0001			<0.0001			<0.0001		
p For sex	<0.0001			<0.0001			<0.0001		

a) Two-way ANOVA was performed using the software package GraphPad Prism 6 for Mac OS X (version 6.0b; GraphPad Software, Inc.) to evaluate effects attributed to curcumin formulation and to sex. The number of observations (*n*) was 13 women and 10 men for the native curcumin and curcumin micelles, and, because of a dropout during the study, nine men for the curcumin micronisate intervention.

large interindividual differences in absorption of native curcumin in men (Table 2). The relative systemic availability of curcumin, as determined by comparing the plasma AUC, was 14, 5, and 9 times higher in women, men, and all subjects, respectively, after ingestion of curcumin micronisate, and 277-, 114-, and 185-fold higher, respectively, following the ingestion of curcumin micelles compared to the native form (Table 2). Relative to native curcumin, C_{max} following micronisate ingestion were 11-, 3-, and 6-fold higher in women, men, and all subjects, respectively, and 806-, 251-, and 453-fold higher after ingestion of curcumin micelles. The micelles, but not the micronisate, significantly reduced the time to reach the maximum plasma concentration (T_{max}) for all three curcuminoids in women and men (Table 2). No sex differences were observed for any of the curcuminoids with respect to C_{max} or T_{max} (Fig. 1 and Table 2).

3.3 Urinary excretion of curcumin, DMC, and BDMC

Cumulative urinary excretion of total curcumin, DMC, and BDMC over 24 h was significantly increased following the consumption of curcumin micronisate and micelles compared to native curcumin and both the formulation and sex significantly affected curcumin excretion (Table 3). The excretion of all three curcuminoids was approximately two to three times higher in women than men (Table 3). The mean percentages of the oral curcumin dose recovered as total curcumin in the 24 h urine samples of all subjects ($n = 23$) were 0.002 ± 0.012, 0.007 ± 0.005, and 0.151 ± 0.082% for native, micronized, and micellar curcumin, respectively.

4 Discussion

Curcumin and related curcuminoids are potent agents in cell culture and animal models, but have so far shown limited biological potency in clinical trials when administered as native compounds [29, 33–35]. This discrepancy is largely attributed to their low oral bioavailability, which results from their poor solubility in the aqueous phase of the digestive fluids, and their rapid intestinal and hepatic metabolism and urinary excretion [2]. We therefore developed two novel curcumin formulations and aimed at testing their absorption kinetics in healthy women and men.

We investigated the relative bioavailability of curcumin from the micronisate and micelles, compared to the native phytochemical, in a single-dose experiment by measuring the peak blood concentration (C_{max}), the time to reach the peak concentration (T_{max}), and the AUC. The AUC is the most reliable measure of the biological availability because it takes into account the entire response over time, whereas $C_{max,}$ which is used by some researchers to describe the "fold-increase in bioavailability," measures only one point in time and is therefore less robust [45].

Table 4. Human trials reporting pharmacokinetic data for native curcumin

Study population	Source	No. of subjects	Dose (g)	T_{max}[a)] (h)	C_{max} (nmol/L)	AUC (nmol/L × h)	CUR analysis	Urinary excretion (nmol/L)	Comments	Ref.
Single oral dose experiments										
Healthy subjects	Capsules of pure curcumin powder	10	2	1	16 ± 14	11	Free curcumin[b)]	n. d.		[28]
Healthy subjects	Capsules of powder extract (curcumin, 75%; DMC, 23%; BDMC, 2%)	12	10 12	3 ± 0.4 7 ± 0.8	8415 ± 1629 6162 ± 3176	95 906 ± 10 261 72 127 ± 8062	Total curcumin[b)]	n. d n. d.	Free curcumin was detected in the plasma of only one subject (30 min. after the ingestion of the 10 g dose)	[30]
Healthy subjects	Capsules of a standardized powder extract (curcumin, 75%; DMC, 23%; BDMC, 2%)	24	0.5 1 2 4 6 8 10 12	n. d n. d n. d n. d n. d n. d 4 2	n. d. n. d. n. d. n. d n. d n. d 137 156	n. d. n. d. n. d. n. d. n. d. n. d. n. d. n. d.	Free curcumin	n. d. n. d. n. d. n. d. n. d. n. d. n. d. n. d.	No curcumin was detected in the serum of subjects administered 0.5–8 g. Low levels of curcumin were detected in two subjects administered 10 or 12 g	[32]
Long-term experiments										
Colorectal cancer patients	Capsules of curcuma extract (curcumin, 90%; DMC, 10%)	15	0.036 0.072 0.108 0.144 0.180 for four months	n. d. n. d. n. d. n. d. n. d.	n. d. n. d. n. d. n. d. n. d.	n. d. n. d. n. d. n. d. n. d.	Total curcumin	n. d. n. d. n. d. n. d. n. d.	144–519 and 64–1054 nmol curcumin/g dried feces, respectively, in day 29 fecal samples of patients consuming 0.144 or 0.180 g/day curcumin	[29]
Patients with precancerous lesions	Capsules of curcumin (99.3%)	25	4 6 8 for three months	2 ± 0.6 2 ± 1.73 2 ± 0.35	510 ± 110 630 ± 60 1770 ± 1870	2550 ± 1760 4800 ± 4490 13740 ± 5630	Free curcumin	n. d. n. d. n. d.		[31]

Table 4. Continued

Study population	Source	No. of subjects	Dose (g)	T_{max}[a)] (h)	C_{max} (nmol/L)	AUC (nmol/L × h)	CUR analysis	Urinary excretion (nmol/L)	Comments	Ref.
Colorectal cancer patients	Capsules of curcuminoids (curcumin, 90%; DMC, 8%; BDMC, 2%)	15	0.45 0.90 1.80 3.60 for four months	n. d. n. d. n. d. 1	n. d. n. d. n. d. 11 ± 0.6	n. d. n. d. n. d. n. d.	Total curcumin	n. d. n. d. n. d. curcumin, 100–1300; curcumin sulfate 19–45; curcumin glucuronide 210–510	Curcumin recovered in feces in all groups	[34]
Patients with hepatic metastatic disease from primary colorectal adenocarcinomas	Capsules of purified turmeric extract (curcumin, 90%; DMC, 6%; BDMC, 4%)	12	0.45 1.8 3.6 for 1 wk	n. d. n. d. n. d.	n. d. n. d. traces	n. d. n. d. n. d.	Total curcumin	n. d. n. d. n. d.	Concentrations below LOQ and near LOD (~3 nmol/L) in patients receiving 3.6 g curcumin The concentrations of curcumin in normal and malignant colorectal tissue of patients receiving 3.6 g of curcumin were 12.7 ± 5.7 and 7.7 ± 1.8 nmol/g, respectively	[33]
Colorectal cancer patients	Capsules of pure curcumin powder (98.0%)	41	2 4 for 30 days	n. d. n. d.	n. d. 213 ± 229	n. d. n. d.	Total curcumin	n. d. n. d.		[35]
Mild-to-Moderate Alzheimer's disease patients	Capsules of powder plant extract (curcuminoids, 95% with curcumin, 70–80%; DMC 15–25%; BDMC, 2.5–6.5%)	30	2 4 for 24 wk	n. d. 3	n. d. 21 ± 9	n. d. n. d.	Free curcumin	n. d. n. d.		[36]

a) AUC, area under the blood concentration-time curve; C_{max}, maximum blood concentration, CUR, curcumin; n. d., not detected; T_{max}, time to reach maximum blood concentration.
b) Free curcumin concentrations were quantified by extraction of the analyte without prior enzymatic hydrolysis of conjugates with β-glucuronidase/sulfatase.
c) Total curcumin concentrations were quantified by extraction of the analyte after prior enzymatic hydrolysis of conjugates with β-glucuronidase/sulfatase.

Table 5. Human trials reporting pharmacokinetic parameters for curcumin formulations aimed at enhancing curcumin bioavailability

Study population	Dosage form	Product name	No. of subjects	Dose (g)	T_{max}[a)] (h)	C_{max} (nmol/L)	AUC (nmol/L × h)	CUR analysis	Urinary excretion	Ref.
Single oral dose experiments										
Healthy subjects	Capsules of pure curcumin powder combined with 0.02 g of pure piperine powder		10	2	0.75	489 ± 434	217 ± 27	Free curcumin[b)]	n. d.	[28]
Healthy subjects	Capsules of curcumin with turmeric essential oils	BCM-95™, Biocurcumax™	11	2	3	1240	8690	Free curcumin	n. d.	[37]
Healthy subjects	Capsules of solid lipid nanoparticles of which, curcumin >60%	Longvida™	6	0.65	2 ± 0.4	61 ± 5	484 ± 74	Free curcumin	n. d.	[41]
Healthy subjects	Capsules of a phosphatidylcholine complex	Meriva™	9	0.209 0.376	4 ± 0.8 3.8 ± 0.6	66 ± 16 1765 ± 34	740 ± 186 1460 ± 355	Total curcumin[c)]	n. d.	[38]
Healthy subjects	Submicron (nano) suspension in water	Theracurmin™	14	0.03	1	80 ± 35	307 ± 166	Total curcumin	n. d.	[39]
Healthy subjects	Capsules of a submicron (nano) suspension	Theracurmin™	6	0.15 0.21	4 4	513 ± 130 747 ± 182	7 ± 950 10 ± 1167	Total curcumin	n. d.	[40]
Patients with osteosarcoma	Capsules of solid lipid nanoparticle of which, curcumin >60%	Longvida™	11	2 3 4	4 ± 0.4 2 ± 0.2 4 ± 1.6	88 ± 11 85 ± 16 111 ± 24	513 ± 33 819 ± 113 1017 ± 74	Free curcumin	n. d.	[41]

a) AUC, area under the blood concentration-time curve; C_{max}, maximum blood concentration; CUR, curcumin; n. d., not detected; T_{max}, time to reach maximum blood concentration.
b) Free curcumin concentrations were quantified by extraction of the analyte without prior enzymatic hydrolysis of conjugates with β-glucuronidase/sulfatase.
c) Total curcumin concentrations were quantified by extraction of the analyte after prior enzymatic hydrolysis of conjugates with β-glucuronidase/sulfatase.

The ingestion of a single oral dose of 500 mg curcuminoids (410 mg curcumin) as micelles resulted in a mean plasma C_{max} of 3228 nmol/L for all study subjects compared to 7 nmol/L after the administration of native curcuminoids. To the best of our knowledge, the hitherto highest published curcumin plasma C_{max} of 8420 nmol/L were achieved with a single oral dose of 10 g curcumin [30], followed by C_{max} of 1770 and 1765 nmol/L after intake of a single oral dose of 8 g native or 376 mg liposomal curcumin ("Meriva"; Table 4) [31, 38]. Only very small amounts of curcumin reach the circulation after oral administration in humans, even when very high doses of native curcumin are administered (Tables 4 and 5). Therefore, solutions to overcome the low bioavailability of curcumin, such as the inhibition of curcumin metabolism with adjuvants as well as novel solid and liquid oral delivery systems, are intensively investigated. Solid lipid nanoparticles and a micronized form of crystalline curcumin have already been introduced to clinical trials [9, 46].

The use of adjuvants, such as piperine [28] or turmeric essential oils [37], enhanced curcumin bioavailability (based on AUC) 20- or 7-fold, respectively (Table 5). Incorporation of curcumin into lecithin (mainly phosphatidylcholine) liposomes resulted in a *ca*. fourfold better absorption (based on AUC) than native curcumin in nine healthy volunteers [38]. The bioavailability of a micronized form of crystalline curcumin ("Theracurmin^{TM}," prepared from curcumin, ghatti gum, and water), compared to native curcumin, was 27-fold increased (Table 5) [39]. Thus, our micellar delivery system, which enhanced curcumin bioavailability 185-fold (all subjects), appears to be superior to all hitherto tested formulations, while our micronisate (ninefold increase in AUC) is similarly effective as previously reported strategies (Table 5). Furthermore, the C_{max} achieved with a single oral dose of 410 mg curcumin from our micellar formulation (women, 3.7 μmol/L; men 2.6 μmol/L) are higher than those observed after the intake of 8 g of native curcumin [31].

The present study revealed sex differences with respect to the plasma AUC of curcumin. Women absorbed curcumin to a larger extent (higher C_{max} and AUC) than men (Table 2). This could be due to the reportedly higher expression and activity of the hepatic drug efflux transporter P-glycoprotein (MDR1) and some isoforms of the glucuronosyltransferases and sulfotransferases, enzymes involved in curcumin biotransformation, in men [47]. However, the differences in bodyweight (Table 1), blood volume, and body fat, which ultimately lead to smaller volumes of distribution in women, may also account for the observed differences [47].

Less than 0.2% of the oral dose of curcumin was excreted with urine within 24 h. Thus, >98.8% of the ingested curcumin was either excreted via the bile and feces or may have been distributed to body tissues where it may potentially exert biological activities.

Free curcumin concentrations as low as 100 nmol/L reversed disease state and reduced IL-1β in Alzheimer's disease models [48, 49], therefore our newly developed curcumin formulations may be suitable vehicles for the delivery of pharmacologically relevant doses of the phytochemical in human intervention trials.

4.1 Concluding remarks

Our newly developed curcumin micronisate and micelles increased the bioavailability of curcuminoids in humans without affecting liver and kidney function. The micellar formulation in particular increased the absorption of curcumin to a hitherto unrivalled extent. These novel formulations may thus be promising new tools to safely deliver the nutraceutical in clinical trials. Further human studies aimed at comparing the bioavailability and therapeutic efficacy of curcumin micelles in young versus aged subjects are under way in our laboratory.

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DB developed and provided the micellar formulation. ST and JJ developed and provided the curcumin micronisate. JF designed and CS and AK conducted the study. CS analyzed data and performed statistical analysis. CS and JF wrote the first draft of the manuscript and all authors read, edited, and approved the final manuscript. JF had primary responsibility for the final content.

Potential conflict of interest statement: DB is the founder and CEO of AQUANOVA AG, the holder of multiple patents on the micellar solubilization technology, and markets the developed curcumin micelles for profit. JJ works and ST worked for a company producing and selling micronisates. The role of the industry partners in this project was solely to develop the curcumin formulations and to provide them in sufficient quantity for the human trial. Data acquisition and interpretation was performed by the authors from the University of Hohenheim. CS, AK and JF have no known conflict of interest.

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