Pharmacokinetics of a Single Dose of Turmeric Curcuminoids Depends on Formulation: Results of a Human Crossover Study

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ABSTRACT
Background: Curcuminoids from turmeric rhizome have significant health benefits but low bioavailability.

Objectives: To assess the pharmacokinetics of a novel natural turmeric dried colloidal suspension compared with 4 other turmeric formulations (including a standardized extract) at their respective recommended dosages.

Methods: Thirty healthy men and women (18 to 45 y old) were enrolled in a randomized, open-labeled, crossover trial, and sequentially consumed single oral doses of standard turmeric extract (1500 mg), liquid micellar preparation (1000 mg), piperine-curcuminoid combination (1515 mg), phytosome formulation (1000 mg), or the dried colloidal suspension (300 mg). Eleven blood samples were obtained over 24 h, plasma was extracted with or without deconjugation with β-glucuronidase or sulfatase, and ultra-high-pressure liquid chromatography/tandem MS was used to quantify the 3 parent curcuminoids and 12 metabolites. Classical pharmacokinetics parameters were derived.

Results: The total AUC values of unconjugated curcuminoids were highly variable within participants, with no significant differences between formulations. However, the AUC values for total curcuminoids (including all metabolites) showed significant product effects. Indeed, the micellar preparation delivered higher levels of total curcuminoids than any other formulation (8540 ng·h/mL), reaching significance when compared with the dried colloidal suspension and standard extract (6520 and 5080 ng·h/mL, respectively). After dose normalization, both micellar and dried colloidal formulations showed significantly higher AUC levels than the standard extract (respectively 136 and 72.9, compared with 3.7 ng·h/mL/mg). Total curcuminoid absorption levels were also significantly higher for the dried colloidal suspension when compared with either piperine or phytosome formulations. Interestingly, no significant differences were observed between the piperine-curcuminoid combination and the standard extract. No serious adverse events were reported.

Conclusions: The administration of a low dose of the novel natural dried colloidal suspension provided high unconjugated and conjugated curcuminoid absorption, with significant beneficial differences when compared with the high dose of standard extract. This trial was registered at clinicaltrials.gov as NCT03621865. J Nutr 2021;00:1–15.

Keywords: absorption, Curcuma longa, curcumin, metabolism, relative bioavailability, metabolites, curcuminoids

Introduction
The rhizome of Curcuma longa (turmeric) is used as a spice, as a traditional medicinal in Asia (1), and also as one of the most popular botanical dietary supplements in the United States (2). Supported by both in vitro and in vivo data, turmeric has antioxidant and anti-inflammatory activities, can stimulate the immune system, and has anticancer activity (3–9). The curcuminoids curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC) are viewed as the most bioactive turmeric constituents associated with its potential health benefits.

Orally administered turmeric native compounds have a low intestinal absorption (10–12), and most are excreted unchanged in the feces (13). This observation is consistent with the poor absorption (0–20%) predicted by the Caco-2 human intestinal epithelial monolayer absorption model (14). Phase I reduction and phase II conjugation (Figure 1) appear to be the primary metabolic pathways of absorbed curcuminoids, taking place in the intestinal and hepatic tissues (15–18). In addition to rapid metabolism, absorbed curcumin is rapidly eliminated from the systemic circulation (5, 12, 15). Curcumin can also be metabolized by an NADPH-dependent
Curcumin/dihydrocurcumin reductase in intestinal microbiota to form dihydrocurcumin (DHC) and tetrahydrocurcumin (THC) (19). THC but not curcumin have been reported to accumulate in rat tissues, suggesting that microbiota could be also a factor in the metabolism and bioavailability of curcuminoids (20).

Curcuminoids are hydrophobic with high solubility in organic solvents (10) but much lower solubility in water. For example, the solubility of curcumin in aqueous buffer (pH 5.0) is only 11 ng/mL (21). As described by FAO in 2004, curcumin also exhibits keto-enol tautomerism, with the favored keto form being stable under acid conditions but insoluble in water, whereas its enol form is soluble in water but unstable above pH 7 (21, 22).

Due to the combination of poor oral absorption, rapid metabolism, and rapid elimination from the systemic circulation, systemic concentrations of unconjugated curcumin do not exceed the low micromolar concentration in humans even after oral doses ≤ 12 g. To enhance the oral bioavailability of curcumin in turmeric extracts, a variety of formulations have been developed and are marketed to consumers. These formulations include liposomal curcumin, nanoparticles containing curcumin, and adjuvants like piperine and phospholipids (15, 17, 23). Unfortunately, few of these formulations have been tested in clinical trials using clinically relevant doses in comparison with a standard turmeric extract containing 95% curcuminoids.

The aim of this study was to assess the bioavailability of 5 formulations of turmeric extract at clinically relevant and recommended dosages for health conditions such as inflammation, joint health, cardiometabolic health, liver health, and cognition (24–31). The pharmacokinetics of curcuminoids in a standardized turmeric extract were compared with a combination containing the adjuvant piperine (inhibits phase II metabolism) (32), and 3 alternatives designed to enhance absorption including a phytosome formulation (33), a liquid micellar preparation (34), and a new dried colloidal suspension. An analytical method was also developed to quantify separately the 3 major turmeric curcuminoids and their phase I and II metabolites in human plasma to support pharmacokinetics modeling and to clarify routes of metabolism.
Methods

Ethics

The protocol and all the documents of the trial were approved by the Committee for Patient Protection (Comité de Protection des Personnes; Ouest V, Rennes, France; reference number 18/050-1) and by the National Agency for Drug Safety (Agence national de sécurité du medicament; registration number 2018_A01390-55). Written informed consent was obtained for all the participants before inclusion in the study.

Study materials

All turmeric supplements for human consumption were encapsulated in hydroxypropyl methylcellulose capsules. The reference product was a standard turmeric powder extract (STE) containing 95% curcuminoids (Naturex) and tested at the recommended efficacy dosage of 1500 mg (1425 mg curcuminoids) in 4 capsules. A phytosome formulation (PHYT) of turmeric extract, phosphatidyl choline, and microcrystalline cellulose (Meriva; Indena) containing 18–22% curcuminoids was administered at a dosage of 1000 mg in 2 capsules (180–220 mg curcuminoids) as recommended by the manufacturer. A dried colloidal suspension (TPG) of standard turmeric extract, quillaja extract, sunflower oil, and acacia gum containing 30% curcuminoids (Turmipure GOLD; Naturex) was tested at a dosage of 300 mg (90 mg curcuminoids) in 1 capsule as directed. A turmeric extract standardized to 95% curcuminoids (C3 complex; Sabinsa) at 1500 mg (1425 mg curcuminoids) combined with 15 mg of a pepper extract standardized to 95% piperine (Bioperine; Sabinsa) was administered in 3 capsules (TEP). A liquid micellar preparation (NOV) containing 6% curcuminoids (NovaSOl; Aquanova AG) was administered at a dosage of 1000 mg (60 mg curcuminoids) in 2 capsules. Ten capsules of each turmeric product were analyzed using ultra-high-pressure liquid chromatography (UHPLC)/tandem MS as described in Supplemental Methods to ascertain the actual quantities of curcuminoids administered (Table 1).

Study design

Volunteers were screened until 30 adult participants were enrolled in a randomized, open-labeled, crossover study following guidelines for appropriate sample size selection in pilot studies (35–40). In chronological order of inclusion, participants were assigned a sequence number by the randomization procedure using SAS software (SAS Institute) from July 2018 to October 2018. The first of the 5 intervention visits, taking place ≤3 wk after the screening visit, also constituted the randomization visit. Each experimental session was separated by 7 to 14 d. Volunteers were not allowed to consume curcumin-containing food supplements or foods (turmeric, curry, etc.) for 2 wk prior to testing and during the study, and had to keep their life habits (eating, physical activity, tobacco and alcohol consumption) stable during the entire study. Taking new medications, especially antibiotics, laxatives, antidepressants, or medications for food supplements containing plant extracts, vitamins, and minerals, was not permitted during the study, except in case of extreme necessity. Participants were also asked to avoid consuming any medication (e.g., paracetamol or ibuprofen) within 24 h prior to each experimental session, not to have a heavy meal or alcohol abuse, nor strenuous physical exercise within 48 h prior to each experimental session, and not to smoke the morning of each experimental session. Finally, participants were asked to keep the same mode of transportation to come to the investigation site.

Turmeric-free meals and snacks were provided to each participant beginning the night before and during each experimental session (meal compositions are detailed in Supplemental Table 2). After a 12-h overnight fast, vital signs were measured prior to time of blood sampling (see study procedures in Figure 2). At each session, any side effects and potential concomitant treatments were recorded.

Sample collection and preparation

Blood was drawn through a catheter in one of the forearm veins. A baseline blood sample was obtained (T – 10 min), followed by the consumption of 1 of the 5 products with 240 mL water (T0). Additional blood samples were drawn at 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 4.00, 6.00, 8.00, and 24.00 h following product consumption (Figure 2). Blood samples (5 mL each) were collected in tubes containing sodium citrate 3.8% (Greiner bio-one), centrifuged at 2200 × g for 15 min at 4 °C, and the plasma was aliquoted into microtubes. Plasma samples were stored at −80 °C until analysis. Water was not permitted 1 h before or after product administration but was allowed at all other times ad libitum.

Extraction of curcuminoids

For deconjugation, plasma (100 μL) was incubated with β-glucuronidase (2500 U; #G8295; Merck) in phosphate buffer (100 mM, pH 6.8, 37 °C), or sulfatase (200 U; #S9626; Merck) in acetate buffer (0.1 M, pH 5.0, 37 °C) for 1 h with constant mixing. Protein precipitation, solid-phase extraction, and filtration was carried out using Captiva EMR-Lipid 96-well plates (Agilent Technologies) as explained in Supplemental Methods.

UHPLC-tandem MS of curcuminoids in plasma

Unconjugated and conjugated curcumin, DMC, BDMC, THC, and HHC concentrations were measured in plasma using UHPLC-tandem MS on an Agilent 6420 triple quadrupole mass spectrometer equipped with a 1290 UHPLC system and electrospray (detailed procedures in Supplemental Methods and Supplemental Tables 3 and 4).

Trial hypotheses and statistical analyses

The study primary end point was the dose-normalized AUC of total plasma curcuminoids (curcumin, DMC, BDMC, plus their metabolites) from 0 to 24 h (AUC 0–24 h/dose; expressed in ng·h/mL/mg). Our hypothesis was that the dose-normalized AUC of total plasma...
curcuminoids for the colloidal suspension TPG would be higher than that observed for the standard extract STE. Secondary outcomes included peak plasma concentration (\(C_{\text{max}}\)), dose-normalized \(C_{\text{max}}\), time to maximum concentration (\(T_{\text{max}}\)), half-life (\(t_{1/2}\)), terminal elimination rate constant (\(k_{2}\)), AUC 0–24h, and AUC 0–8h. The total AUC values were determined for plasma-specific major curcuminoids and metabolites as well as for total curcuminoids (see Supplemental Methods for a detailed description of the statistical methods used and details on the mixed models).

Statistical analyses were performed using SAS software version 9.3 (SAS Institute) on the intent-to-treat (ITT) population (including all randomly assigned participants in the study, who consumed each study product regarding their randomization sequence, \(n = 30\)). Because similar results were observed on the per-protocol population (participants who presented no major protocol deviations, \(n = 29\)) the corresponding analyses are not presented here. Pharmacokinetic parameters were calculated using R software version 3.5.1 (ncappc package, noncompartmental method) for all tested formulations. Results are expressed as observed mean ± SD. Analyses were performed on log-transformed data to preserve study end-point normality and/or homoscedasticity (assumptions of normality and homoscedasticity for linear models were investigated by graphical representations of residuals produced by statistical models), and multiple pairwise comparisons between products were performed only if a significant product effect was observed. In this case, Tukey adjustment was used to calculate adjusted \(P\) values from the models, and the level of significance was taken to be \(P < 0.05\). In regard to the primary outcome of the study and for clarity, multiple comparisons shown in this manuscript are using either the novel dried colloidal suspension TPG or the reference standard extract STE as main comparatives.

Results

Participant demographics and study materials

Forty-two volunteers were screened, 6 declined to participate, 6 were disqualified due to health considerations, and 30 were enrolled in the study (Figure 3). All 30 of the participants (14 men and 16 women) completed the study, and no serious adverse events were reported after randomization. The mean age of the participants was 33.6 ± 6.8 y, the mean BMI was 22.1 ± 2.1 kg/m², and all blood chemistry and physical examination values were normal (Table 2). The daily dosages of specific curcuminoids in each formulation were determined using UHPLC-tandem MS. In all cases, the total curcuminoid concentrations were in accordance with the nominal values reported on the product labels (Table 1).

All visits for all participants (\(n = 30\)) and 1648/1650 plasma time points were included in the analyses on the ITT population (see Supplemental Methods for kinetics missing data handling). The concentrations of total curcuminoids (curcumin, BMC, DBMC, and their metabolites) in plasma over time after oral administration of each of the 5 curcuminoid formulations were plotted (Figure 4A) and also expressed using a box plot to show variability in the study population (Figure 5A). No significant visit effect was identified for AUC 0–24h of total curcuminoids (\(P = 0.23\)) nor for dose-normalized AUC 0–24h of total curcuminoids (\(P = 0.23\)). Consequently, analyses were performed on all visits. However, some statistically significant visit effects were identified for individual curcuminoids or metabolites or secondary outcomes and are listed in Supplemental Table 5; therefore, for those parameters, data analysis was performed on visit 1 only.

The proportions of individual metabolites after absorption

The methods developed for this study allowed the quantification of 15 individual curcuminoids, as well as various groups of these curcuminoids regarding their biochemical properties (Figure 1). Therefore, the proportions of individual metabolites and sum of the major groups expressed in percentages were calculated as the ratio of the AUC 0–24h of the compound or group of compounds of interest divided by the AUC 0–24h of total curcuminoids for the 5 formulations (Table 3). Plasma concentrations of unconjugated and conjugated curcuminoids indicate high interindividual variability. Interestingly, unconjugated curcumin and parent curcuminoids were minor, representing only 1.1% and 1.3%, respectively, of all metabolites quantified in plasma for the standard extract formulation STE. These proportions did not vary significantly for the other formulations.

The sum of all parent curcuminoids including their glucuronide and sulfate metabolites ranged from 15.5% to 29.4% of the total metabolites, with greater proportions due to curcumin and its conjugated forms, with DMC and BDMC metabolites being less abundant (Table 3). Due to undetectable concentrations for most participants and formulations, the model could not estimate any pharmacokinetic parameters for the reduced forms of curcumin, THC and HHC (phase I
FIGURE 3  Clinical study CONSORT diagram. A total of 42 volunteers were screened, of which 12 did not meet the inclusion/exclusion criteria. Thirty participants were enrolled and completed the study. No participants discontinued the intervention, were lost to follow-up, or were excluded from the data analysis. No serious adverse events were reported.

metabolites). On the other hand, THC glucuronide and THC sulfate represented a high proportion of the total metabolites, varying respectively from 26% to 35.8% and 3.2% to 7%. Unexpectedly, and for all tested formulations, the plasma concentrations of the glucuronic acid and sulfate phase II conjugates of curcumin and all other curcuminoids were considerably higher than those of the unconjugated forms, with the sulfate conjugates usually predominating over the glucuronides. These results highlight the diversity of systemic curcuminoids after consumption of turmeric formulations (Table 3).

Pharmacokinetics of unconjugated curcuminoids
Although unconjugated curcumin, DMC, and BDMC are commonly used to compare turmeric preparations, the 5 tested formulations did not differ in AUC 0–24h or Cmax

| TABLE 2  | Demographics and biological data of study participants at screening¹ |
|-----------|---------------------------------------------------------------|
|           | All participants (n = 30) | Men (n = 14) | Women (n = 16) |
| Age, y    | 33.6 ± 6.79 | 36.7 ± 5.50 | 30.8 ± 6.75 |
| Height, cm| 170 ± 10.3  | 179 ± 5.15  | 163 ± 8.16  |
| Weight, kg| 64.5 ± 11.1 | 72.8 ± 8.33 | 57.3 ± 7.61 |
| BMI, kg/m²| 22.1 ± 2.13 | 22.8 ± 2.45 | 21.4 ± 1.61 |
| Systolic blood pressure, mmHg | 124 ± 15 | 127 ± 15 | 121 ± 14 |
| Diastolic blood pressure, mmHg | 75 ± 9 | 78 ± 10 | 72 ± 7 |
| Heart rate, bpm | 66 ± 11 | 63 ± 11 | 69 ± 11 |
| Glucose, g/L | 0.91 ± 0.079 | 0.96 ± 0.070 | 0.87 ± 0.063 |
| Creatinine, μmol/L | 67.0 ± 11 | 75.1 ± 9.62 | 60.0 ± 6.24 |
| Urea, mmol/L | 4.02 ± 1.04 | 4.19 ± 0.974 | 3.86 ± 1.10 |
| SGPT, μkat/L | 0.34 ± 0.244 | 0.47 ± 0.236 | 0.23 ± 0.193 |
| SGOT, μkat/L | 0.35 ± 0.119 | 0.40 ± 0.113 | 0.31 ± 0.109 |
| γ-GT, μkat/L | 0.35 ± 0.333 | 0.52 ± 0.425 | 0.20 ± 0.087 |
| Leukocytes, 10⁹/L | 6.34 ± 1.41 | 6.51 ± 1.74 | 6.19 ± 1.09 |
| Erythrocytes, 10¹²/L | 4.59 ± 0.382 | 4.80 ± 0.408 | 4.41 ± 0.253 |
| Hemoglobin, g/dL | 14.4 ± 1.05 | 15.2 ± 0.91 | 13.7 ± 0.57 |
| Hematocrit, % | 42.6 ± 3.31 | 45.0 ± 2.71 | 40.4 ± 2.05 |
| Platelets, 10⁹/L | 258 ± 66.7 | 236 ± 49.1 | 278 ± 75.3 |
| Lymphocytes, 10⁹/L | 2.05 ± 0.437 | 2.06 ± 0.501 | 2.04 ± 0.389 |
| Monocytes, 10⁹/L | 0.54 ± 0.196 | 0.54 ± 0.215 | 0.49 ± 0.174 |
| Basophils, 10⁹/L | 0.072 ± 0.026 | 0.068 ± 0.0236 | 0.075 ± 0.0283 |
| Polynuclear neutrophils, 10⁹/L | 3.47 ± 1.26 | 3.54 ± 1.52 | 3.41 ± 1.03 |
| Mean corpuscular volume, fl | 92.8 ± 3.94 | 94.2 ± 4.36 | 91.7 ± 3.22 |
| MCHC, g/dL | 33.8 ± 0.65 | 33.7 ± 0.71 | 33.9 ± 0.60 |
| Erythrocyte distribution width, % | 13.7 ± 1.23 | 13.7 ± 0.77 | 13.6 ± 1.55 |
| Mean platelet volume, fl | 9.48 ± 1.04 | 9.56 ± 1.03 | 9.41 ± 1.08 |

¹Values are means ± SD. MCHC, mean corpuscular hemoglobin concentration; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; γ-GT, gamma-glutamyltransferase.
FIGURE 4 Twenty-four hour kinetics of plasma total curcuminoids after consumption of a single dose of the turmeric formulations STE, TEP, PHYT, NOV, and TPG by healthy human participants. (A) Concentrations of total curcuminoids; and (B) dose-normalized concentrations of total curcuminoids determined using UHPLC-tandem MS. Observed means ± SD on the ITT population, n = 30 for each formulation. Total curcuminoids = curcumin + curcumin sulfate + curcumin glucuronide + DMC + DMC sulfate + DMC glucuronide + BDMC + BDMC glucuronide + BDMC sulfate + THC + THC sulfate + THC glucuronide + HHC + HHC glucuronide + HHC sulfate. BDMC, bisdemethoxycurcumin; DMC, desmethoxycurcumin; HHC, hexahydrocurcumin; ITT, intent-to-treat; NOV, liquid micellar formulation; PHYT, phytosome formulation; STE, standard turmeric extract; TEP, piperine-curcuminoids combination; THC, tetrahydrocurcumin; TPG, Turmipure Gold formulation; UHPLC, ultra-high-pressure liquid chromatography.

Pharmacokinetics of curcumin metabolites
This group of curcuminoids includes curcumin, its reduced forms THC and HHC (phase I metabolites), and all their respective glucuronic acid and sulfate conjugates (phase II metabolites). In fact, these 9 compounds together represented ∼90% of plasma curcuminoids after turmeric formulation consumption (Table 3). When looking at conjugate plasma concentrations in the tested formulations for curcumin, THC, and HHC, both glucuronide and sulfate forms demonstrated significant differences with either the standard turmeric extract STE or the new colloidal suspension TPG (Tables 5 and 6). The plasma glucuronides of curcumin, THC, and HHC varied respectively from 3.5% to 6.1%, 26% to 35.8%, and 13.9% to 22.2% between all tested formulations (Table 3). When using the standard turmeric extract STE as a reference, the micellar preparation NOV led to significantly higher glucuronide AUC 0–24h and Cmax for curcumin, THC, and HHC (all P < 0.05). In contrast, the phytosome formulation PHYT glucuronide AUC 0–24h and Cmax were significantly lower for curcumin, THC, and HHC (all P < 0.05). Despite similar levels for curcumin glucuronide and THC glucuronide with the standard turmeric extract STE, the new colloidal
FIGURE 5  AUC 0–24h of plasma total curcuminoids after consumption of a single dose of the turmeric formulations STE, TEP, PHYT, NOV, and TPG by healthy human participants. (A) AUC 0–24h of total curcuminoids; and (B) dose-normalized AUC 0–24h of total curcuminoids determined using UHPLC-tandem MS. Boxplot representing the group medians, 25th and 75th percentiles, minima, and maxima of observed means on the ITT population, \( n = 30 \) for each formulation. †Significantly different from the reference STE product, \( P < 0.0001 \). $,#Significantly different compared with the TPG product: $ \( P < 0.05 \), #\( P < 0.0001 \). Total curcuminoids = curcumin + curcumin sulfate + curcumin glucuronide + DMC + DMC sulfate + DMC glucuronide + BDMC + BDMC glucuronide + BDMC sulfate + THC + THC sulfate + THC glucuronide + HHC + HHC glucuronide + HHC sulfate. BDMC, bisdemethoxycurcumin; DMC, desmethoxycurcumin; HHC, hexahydrocurcumin; ITT, intent-to-treat; NOV, liquid micellar formulation; PHYT, phytosome formulation; STE, standard turmeric extract; TEP, piperine-curcuminoids combination; THC, tetrahydrocurcumin; TPG, Turmipure Gold formulation; UHPLC, ultra-high-pressure liquid chromatography.

The plasma sulfate conjugate proportions of total curcuminoids quantified in all tested formulations represented 7.1% to 12.5%, 3.2% to 7%, and 22.7% to 28%, respectively, for curcumin, THC, and HHC (Table 3). The comparisons with the standard turmeric extract STE showed significantly higher sulfate conjugate levels of curcumin (only Cmax, \( P < 0.05 \)) and HHC (AUC 0–24h and Cmax, \( P < 0.0001 \)) for the micellar preparation NOV. Inversely, the phytosome formulation PHYT produced significantly lower levels than did the standard turmeric extract STE for the sulfate forms of THC (only Cmax, \( P < 0.05 \)) and HHC (AUC 0–24h and Cmax, \( P < 0.0001 \)). Similar to the glucuronide forms, the novel colloidal suspension TPG produced significantly higher sulfate levels for HHC (AUC 0–24h and Cmax, \( P < 0.0001 \)) than the standard turmeric extract STE. The colloidal suspension TPG also showed significantly higher sulfate levels than the phytosome formulation PHYT for THC (Cmax, \( P < 0.05 \)) and HHC (AUC 0–24h and Cmax, \( P < 0.0001 \)), as well as significantly higher levels when compared with the piperine-curcuminoids combination (TEP) for HHC sulfate (AUC 0–24h and Cmax, \( P < 0.0001 \); Table 6).

In contrast to studying only unconjugated curcuminoids, this study of 9 curcumin metabolites individually and as a group, allowed the clear distinction between all the turmeric formulations tested over 24 h after consumption. Indeed,
when compared with both the standard extract STE and the colloidal suspension TPG, significantly lower absorption levels were observed for the phytosome formulation PHYT (AUC 0–24h and Cmax, P < 0.0001), and higher absorption levels for the micellar preparation NOV (AUC 0–24h and Cmax compared with STE and Cmax only compared with TPG, all P < 0.0001). Importantly, in addition to higher absorption levels than the phytosome formulation PHYT, these results demonstrated superior AUC 0–24h and Cmax for the micellar suspension TPG when compared with both the standard extract STE and the piperine-curcuminoid combination TEP (all P < 0.05; Table 7).

**Pharmacokinetics and bioavailability of total curcuminoids**

This group of curcuminoids encompasses all the parents, reduced (phase I) and conjugated (phase II) compounds, which together represent 15 curcuminoids (curcumin, curcumin sulfate, curcumin glucuronide, DMC, DMC sulfate, DMC glucuronide, BDMC, BDMC glucuronide, BDMC sulfate, THC, THC sulfate, THC glucuronide, HHC, HHC glucuronide, and HHC sulfate). Plasma AUC 0–24h and Cmax ranges fluctuated respectively from 2330 to 8540 ng/mL and 209 to 1760 ng/mL (Figures 4A and 5A; Table 7), showing significant variations between the different formulations when compared with either the standard extract STE or the colloidal suspension TPG. Indeed, the micellar preparation NOV displayed significantly higher AUC 0–24h and Cmax than did the standard extract STE, whereas the phytosome formulation PHYT had significantly lower AUC 0–24h and Cmax (all P < 0.0001). Significant differences were observed with the colloidal suspension TPG when compared with the micellar preparation NOV (AUC 0–24h and Cmax, P < 0.05). However, the new colloidal suspension TPG brought significantly higher concentrations of plasma total curcuminoids than did the phytosome formulation PHYT, the piperine-curcuminoid combination TEP (AUC 0–24h and Cmax, all P < 0.05), or the standard extract STE (Cmax only, P < 0.05) (Table 7).

The primary study end point defined for this clinical trial was the dose-normalized AUC 0–24h of total plasma curcuminoids (expressed in ng-h/mL/mg), observable for all formulations in Figures 4B and 5A, and tabulated in Table 7. After dose normalization, plasma concentrations and corresponding AUC 0–24h of total curcuminoids were significantly lower for the standard extract STE than for the micellar preparation NOV, the phytosome formulation PHYT, or the colloidal suspension TPG (all P < 0.0001). Despite significantly higher AUC 0–24h and Cmax for the micellar preparation NOV (all P < 0.0001), it is interesting to highlight that the total curcuminoid concentrations observed after dose normalization confirmed greater pharmacokinetics AUC 0–24h and Cmax for the new colloidal suspension TPG than for the phytosome formulation PHYT or the piperine-curcuminoid combination TEP (all P < 0.0001). Importantly, the significantly higher

**TABLE 3** Contribution of the different curcuminoids to the total metabolites after consumption of a single dose of the turmeric formulations STE, TEP, PHYT, NOV, and TPG by healthy human participants

| Considered curcuminoids (no. of metabolites), % | STE | TEP | PHYT | NOV | TPG |
| --- | --- | --- | --- | --- | --- |
| Curcumin (1) | 1.1 | 1.2 | 1.6 | 0.3 | 0.9 |
| DMC (1) | 0.1 | 0.6 | 0.3 | 0.0 | 0.1 |
| BDMC (1) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Curcumin + DMC + BDMC (3) | 1.3 | 1.8 | 1.9 | 0.3 | 1.1 |
| Curcumin glucuronide (1) | 4.6 | 4.3 | 6.1 | 5.7 | 3.5 |
| DMC glucuronide (1) | 0.8 | 0.8 | 2.7 | 1.0 | 0.4 |
| BDMC glucuronide (1) | 0.1 | 0.1 | 0.3 | 0.1 | 0.0 |
| Curcumin sulfate (1) | 12.2 | 10.8 | 12.5 | 7.1 | 8.8 |
| DMC sulfate (1) | 2.3 | 2.5 | 5.2 | 0.8 | 1.5 |
| BDMC sulfate (1) | 0.8 | 0.8 | 0.8 | 1.2 | 0.1 |
| Sum of parent compounds and their relative glucuronide and sulfate metabolites (9) | 22.1 | 21.1 | 29.4 | 16.2 | 15.5 |
| THC (1) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| THC glucuronide (1) | 26.0 | 28.1 | 27.0 | 25.8 | 31.2 |
| THC sulfate (1) | 6.3 | 6.0 | 7.0 | 3.5 | 3.2 |
| HHC (1) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| HHC glucuronide (1) | 18.6 | 16.8 | 13.9 | 21.0 | 22.2 |
| HHC sulfate (1) | 27.0 | 28.0 | 22.7 | 23.6 | 28.0 |
| Curcumin and all its metabolites (9) | 95.8 | 95.3 | 90.9 | 96.9 | 97.8 |
| Total curcuminoids (15) | 100 | 100 | 100 | 100 | 100 |

1. All proportions (expressed as percentage of total curcuminoids) were calculated as the ratio of the AUC 0–24h of the group or compound of interest divided by the AUC 0–24h of total curcuminoids × 100. BDMC, bisdemethoxycurcumin; DMC, demethoxycurcumin; HHC, hexahydrocurcumin; NOV, liquid micellar formulation; PHYT, phytosome formulation; STE, standard turmeric extract; TEP, piperine-curcuminoids combination; THC, tetrahydrocurcumin; TPG, Turmipure Gold formulation.
2. Sum of curcuminoids and their relative glucuronide and sulfate metabolites = curcumin + curcumin sulfate + curcumin glucuronide + DMC + DMC sulfate + DMC glucuronide + BDMC + BDMC glucuronide + BDMC sulfate.
3. Curcumin and all its metabolites = curcumin + curcumin sulfate + curcumin glucuronide + THC + THC sulfate + THC glucuronide + HHC + HHC glucuronide + HHC sulfate.
4. Total curcuminoids = curcumin + curcumin sulfate + curcumin glucuronide + DMC + DMC sulfate + DMC glucuronide + BDMC + BDMC glucuronide + BDMC sulfate + THC + THC sulfate + THC glucuronide + HHC + HHC glucuronide + HHC sulfate.
### Table 4

| Formulation | DMC | BDMC | Curcumin DMC BDMC | NOV | TPG | NOV | TPG | PHYT | NOV | TPG | NOV | TPG |
|-------------|-----|------|------------------|-----|-----|-----|-----|------|-----|-----|-----|-----|
| Time to maximum concentration (Tmax) | 12.3 ± 1.8 | 15.3 ± 0.6 | 12.3 ± 1.8 | 15.3 ± 0.6 | 12.3 ± 1.8 | 15.3 ± 0.6 | 12.3 ± 1.8 | 15.3 ± 0.6 | 12.3 ± 1.8 | 15.3 ± 0.6 | 12.3 ± 1.8 | 15.3 ± 0.6 |
| AUC 0–24h, ng·h/mL/mg | 0.00 ± 0.00 | 1.47 ± 0.87 | 0.00 ± 0.00 | 1.47 ± 0.87 | 0.00 ± 0.00 | 1.47 ± 0.87 | 0.00 ± 0.00 | 1.47 ± 0.87 | 0.00 ± 0.00 | 1.47 ± 0.87 | 0.00 ± 0.00 | 1.47 ± 0.87 |
| Cmax 0–24h normalized, ng/mL/mg | 0.00 ± 0.00 | 1.22 ± 0.69 | 0.00 ± 0.00 | 1.22 ± 0.69 | 0.00 ± 0.00 | 1.22 ± 0.69 | 0.00 ± 0.00 | 1.22 ± 0.69 | 0.00 ± 0.00 | 1.22 ± 0.69 | 0.00 ± 0.00 | 1.22 ± 0.69 |
| Terminal elimination rate constant (λz) | 0.1 ± 0.1 | 1.31 ± 0.0 | 0.1 ± 0.1 | 1.31 ± 0.0 | 0.1 ± 0.1 | 1.31 ± 0.0 | 0.1 ± 0.1 | 1.31 ± 0.0 | 0.1 ± 0.1 | 1.31 ± 0.0 | 0.1 ± 0.1 | 1.31 ± 0.0 |

### Discussion

Unlike previous human pharmacokinetic studies of curcuminoids, this investigation is unique in that it compares multiple curcuminoid formulations available on the market at their daily recommended dosages. Comparing the 5 formulations at exactly the same curcuminoid dosage could have been scientifically meaningful. However, the approach described here is consistent and of interest for consumers, because curcuminoid bioavailability for each formulation has been assessed at dosages relevant to the consumer. Therefore, in addition to the specific ingredient contents, consumers will be able to make informed decisions regarding which turmeric formulation to choose based on their real curcuminoid absorption capacity. Another unique aspect of this investigation is that multiple pharmacokinetic parameters were measured for the 3 most abundant curcuminoids in turmeric (curcumin, BMC, and BDMC) as well as their major metabolites. A new method was specifically developed to allow quantification of numerous metabolites formed from these 3 curcuminoids and to understand better the curcuminoid bioavailability and metabolic transformation after oral administration of the different formulations.

The objective of this study was to assess the pharmacokinetics of a new natural turmeric dried colloidal suspension, TPG, to allow comparisons with the other turmeric formulations, NOV, TEP, PHYT, and a standard turmeric extract, STE, at their recommended dosages. Primary outcome of this trial validated our hypothesis that administration of 300 mg TPG would result in higher absorption levels of total curcuminoids after dose normalization, when compared with 1500 mg STE. In addition, comparisons of pharmacokinetics between each formulation allowed the estimation of curcuminoids total curcuminoids AUC 0–24h after dose normalization for the new colloidal suspension TPG, when compared with the standard extract STE, validated the primary hypothesis of this trial.

### Other pharmacokinetic parameters

In addition to AUC and Cmax, Tmax, t1/2, and λz were determined. In addition to producing higher AUC and Cmax for total curcuminoids, the micellar NOV and colloidal TPG formulations reduced Tmax values, notably for glucuronides of curcumin metabolites, sulfate conjugates of curcumin and HHC, and for total curcuminoids (Tables 5–7). After absorption, total curcuminoids showed shorter t1/2 values of 337 ± 279 and 318 ± 154 min for the micellar NOV and colloidal TPG formulations, respectively, compared with the standard extract STE (t1/2 = 788 ± 1230 min, < P = 0.05) (Table 7). Although the t1/2 of total curcuminoids was shorter for the micellar NOV and colloidal TPG formulations, systemic concentrations were significantly higher before (all P < 0.05), and after dose normalization (all P < 0.0001), especially considering smaller curcuminoid doses compared with the standard extract STE (respectively 95.4% and 93.5% lower; Tables 1 and 7).

The effect of sex was investigated for all of the pharmacokinetic parameters. No significant formulation–sex interaction was identified for AUC 0–24h of total curcuminoids or the individually quantified metabolites. A formulation–sex interaction was observed for Cmax of total curcuminoids (P < 0.05), and both Cmax and Tmax for total curcumin metabolites and HHC glucuronide (P < 0.05).
| Parameter                        | STE       | TEP      | PHYT     | NOV      | TPG    |
|---------------------------------|-----------|----------|----------|----------|-------|
| Cmax (ng/mL)                    | 1140 ± 77.6 | 1140 ± 63.1 | 395 ± 39.5 | 348 ± 155 | 561 ± 489 |
| AUC0–8h normalized (ng·h/mL)    | 236 ± 170 | 235 ± 187 | 214 ± 214†,# 226 | 214 ± 141 | 214 ± 986 |
| AUC0–24h normalized (ng·h/mL)   | 1110 ± 105 | 1046 ± 90.6 | 281 ± 223  | 986 ± 1320 | 973 ± 1150 |
| Tmax, min (h)                   | 277 ± 285 | 277 ± 289 | 277 ± 287 | 277 ± 287 | 277 ± 287 |
| Half-life, min (h)              | 2100 ± 1970 | 2360 ± 3040 | 6930 ± 2230 | 3570 ± 730 | 330 ± 330†,# 491 |
| Relative bioavailability (%)    | 1.07 ± 0.44 | 4.26 ± 3.0 | 6.65 ± 60.8 | 0.86 ± 1.1 | 0.86 ± 1.1 |
| Relative bioavailability (%) 0–8h | 0.04 ± 0.0 | 0.00 ± 0.0 | 0.00 ± 0.0 | 0.00 ± 0.0 | 0.00 ± 0.0 |
| Relative bioavailability (%) 0–24h | 1.07 ± 0.44 | 4.26 ± 3.0 | 6.65 ± 60.8 | 0.86 ± 1.1 | 0.86 ± 1.1 |

Values are means ± SD. Different subscripts (a, b, c) indicate significant differences between treatments (P < 0.05). 

Curcumin glucuronide THC glucuronide HHC glucuronide

Due to limited curcumin absorption, it is commonly observed that pharmacokinetic studies of turmeric formulations intended to demonstrate improved bioavailability have used either a substantial dose of the product or a very low dose of their comparative (e.g., STE). As an example, Schiborr et al. (34) reported bioavailability enhancement for the micellar preparation, though the dosages used were much higher than those recommended by the manufacturers. Participants were administered 7519 mg of the micellar preparation NOV and only 526 mg standard turmeric extract STE (containing 500 mg curcuminoids). In these experimental settings, it is not surprising to observe that relative plasma concentrations of curcumin were 185-fold higher for the micellar preparation NOV than for the standard extract STE. In our study, participants consumed the same product according to the manufacturer’s recommendations, that is, 1000 mg containing 62.7 mg curcuminoids, as well as a recommended efficacy dosage of 1500 mg of standard extract STE. By using this lower dosage (1000 mg compared with 7519 mg), our results showed an improvement in the curcumin bioavailability of only 35.5-fold instead of 185-fold relative to the standard extract STE. Other studies have also shown that curcuminoid relative bioavailability varies with the given doses. Cuomo et al. (33) showed that the phytosome formulation provided 27-fold higher relative absorption of curcumin and its conjugates when administering 209 mg curcuminoids, increasing to 32-fold higher relative absorption at a dosage of 376 mg curcuminoids. In the present study, the phytosome formulation PHYT, given at a dosage containing 179 mg curcuminoids, increased bioavailability of curcumin and its conjugates 5.5-fold relative to the standard extract STE (data not shown). In another study, Kumar et al. (41) found that the relative bioavailability of unconjugated curcuminoids increased 46-fold and 25-fold when administering 391 mg and 97.7 mg of curcuminoids, respectively. In the present study, commercial formulations were compared as marketed and used by consumers, thus limiting bias in the bioavailability evaluation due to specific unusual and unlikely usable dosages.

Another important result of this investigation concerns the piperine-curcuminoid combination TEP, which has been reported to enhance absorption and increase systemic concentration of curcumin in rats and humans (42). Piperine is a well-known inhibitor of drug metabolism, including glucuronidation, and can alter the bioavailability of many drugs (32). However, our results showed that the piperine-curcuminoid combination TEP did not improve curcuminoid bioavailability with respect to unconjugated curcumin, the 3...
Table 6  Pharmacokinetic parameters and relative bioavailabilities of sulfatated curcumin metabolites (curcumin, THC, and HHC) after consumption of a single dose of the turmeric formulations STE, TEP, PHYT, NOV, and TPG by healthy human participants.

|                | STE   | TEP   | PHYT  | NOV   | TPG   |
|----------------|-------|-------|-------|-------|-------|
| Tmax (min)     | 15    | 13.6  | 18.1  | 18.1  | 18.6  |
| Cmax (ng/mL)   | 18–21.5  | 18.6  | 21.5  | 18.1  | 16.5  |
| AUC0–24h, ng/mL | 0.17  | 0.20  | 0.15  | 0.15  | 0.15  |
| AUC0–8h, ng/mL | 0.19  | 2.01  | 0.30  | 0.30  | 0.30  |
| Amax (ng/h/mg) | 1.01  | 1.10  | 1.01  | 1.01  | 1.01  |
| t1/2 (h)       | 10.0  | 3.24  | 2.73  | 2.73  | 2.73  |
| Relative bioavailability | 0.86 | 0.60 | 1.08 | 1.08 |

*Statistically significant compared with the reference STE product; †P < 0.05, ‡P < 0.001, ††P < 0.0001.

Formulation influences curcuminoid bioavailability. To date, there is no consensus whether the activities of turmeric extract are due to unconjugated curcumin, DMC, or BDMC, or to their phase I and phase II metabolites. A review of in vitro studies comparing the antioxidant, anti-inflammatory, antimutagenic, anti-diabetic, and anticarcinogenic activities of BDMC, DMC, and curcumin reported 11 references showing BDMC was less active, 11 indicating BDMC was more active, and 4 showing that BDMC, DMC, and curcumin were equivalent (23). This review also reported that THC was more potent than curcumin, 1 study showed equal potency, and 8 studies showed lower potency. Among the few studies that have investigated the activities of curcumin conjugates, Ireson et al. (46) showed that curcumin sulfate was less effective than unconjugated curcumin in reducing phorbol ester–induced PGE2 production.

Parent curcuminoids, the 9 curcumin metabolites, or even the 15 total curcuminoids evaluated. The different outcomes published in the previous study by Shoba et al. (42) could be attributed to the smaller number of participants (8 instead of 30), the shorter kinetic duration (3 h compared with 24 h in the present study, in which the Tmax of unconjugated curcumin was 6 h), and the quantification of only 1 instead of 15 curcuminoids.

Based on the individual quantification of 15 curcuminoid metabolites, this study demonstrated that unconjugated curcumin, DMC, and BDMC represented only 1% of the total plasma curcuminoids following oral administration of a variety of turmeric formulations. Therefore, curcumin plasma concentration reached a maximum of 18–21.5 ng/mL in contrast to >400 ng/mL for all metabolites combined. Although glucuronic acid and sulfate conjugates of curcumin, DMC, and BDMC represented ~20% of the total curcuminoids found in blood, THC glucuronide, THF sulfate, HHC glucuronide, and HHC sulfate were identified as the most abundant metabolites in human plasma. Interestingly, unconjugated THC and HHC were not detected (Table 3). Previous studies addressing the effects of various formulations on bioavailability only measured unconjugated curcumin, DMC, and BDMC. Besides ignoring the majority of curcuminoids, the former approach would tend to underestimate relative bioavailability. For example, Gota et al. (43) detected no significant unconjugated curcumin in human plasma following oral administration of the standard extract containing 95% curcuminoids and therefore could not calculate the corresponding AUC or relative bioavailability. Antony et al. (44) reported bioavailability enhancement of 6.93-fold with respect to unconjugated curcumin (although the difference in AUC values were not statistically tested) when comparing a curcuminoids—essential oil combination with a standard extract. A more recent study by Jäger et al. (45) included 53% of the metabolites evaluated in the present investigation and found the relative bioavailability of the same curcuminoids—essential oil combination enhanced only 1.3-fold. For comparison, we found that the relative bioavailability of the colloidal suspension TPG over 8 h is 342-fold higher than the standard turmeric extract STE when only unconjugated curcumin is considered (no statistical difference on AUC 0–8h and Cmax; Table 4). This value is reduced to 30.6-fold, but reached significance when total curcuminoids are considered (both AUC 0–8h and Cmax, P < 0.05; Table 7). Altogether, this extended set of data highlights the necessity to consider not only unconjugated curcumin, but also a wider range of metabolites to assess the bioavailability of curcuminoids.

The characterization of each curcuminoid proportional bioavailability, based on 5 different turmeric formulations, drew new perspectives regarding our understanding of their biological efficacy. To date, there is no consensus whether the activities of turmeric extract are due to unconjugated curcumin, DMC, or BDMC, or to their phase I and phase II metabolites. A review of in vitro studies comparing the antioxidant, anti-inflammatory, antimutagenic, anti-diabetic, and anticarcinogenic activities of BDMC, DMC, and curcumin reported 11 references showing BDMC was less active, 11 indicating BDMC was more active, and 4 showing that BDMC, DMC, and curcumin were equivalent (23). This review also reported that 13 studies indicated that THC was more potent than curcumin, 1 study showed equal potency, and 8 studies showed lower potency. Among the few studies that have investigated the activities of curcumin conjugates, Ireson et al. (46) showed that curcumin sulfate was less effective than unconjugated curcumin in reducing phorbol ester–induced PGE2 production.
### TABLE 7 Pharmacokinetic parameters and relative bioavailabilities of total curcuminoids, 3, 9, and 15 metabolites, after consumption of a single dose of the turmeric formulations STE, TEP, PHYT, NOV, and TPG by healthy human participants

| Metabolites quantified, n | Total parent curcuminoids | Total curcumin metabolites | Total curcuminoids |
|--------------------------|----------------------------|-----------------------------|--------------------|
|                          | STE | TEP | PHYT | NOV | TPG | STE | TEP | PHYT | NOV | TPG | STE | TEP | PHYT | NOV | TPG |
| AUC 0–8h, ng h/mL       | 36.2 ± 8.9 | 37.1 ± 13.8 | 36.1 ± 81.4 | 13.9 ± 50.6 | 39.9 ± 99.8 | 2100 ± 1090 | 1620 ± 719* | 854 ± 816* | 5030 ± 1190* | 3330 ± 1110* | 2200 ± 1110 | 1730 ± 723* | 738 ± 681* | 5130 ± 1200* | 3410 ± 1140* |
| AUC 0–24h, ng h/mL      | 64.4 ± 323 | 80.3 ± 176 | 44.2 ± 81.7 | 27.8 ± 88.8 | 69.6 ± 139 | 4860 ± 2380 | 4170 ± 2335* | 2110 ± 1660* | 8020 ± 2343* | 6370 ± 2250* | 5080 ± 2410 | 4380 ± 2335* | 2320 ± 1730* | 8540 ± 2550* | 6520 ± 2280 |
| Tmax, min               | 1130 ± 2510 | 2190 ± 5220 | 1680 ± 2780 | 647 ± 883 | 615 ± 1130 | 2904 ± 1795 | 304 ± 344 | 379 ± 249* | 620 ± 177* | 192 ± 143 | 257 ± 182 | 330 ± 341 | 375 ± 249* | 61.0 ± 16.5* | 190 ± 148 |
| Terminal elimination rate constant, ng/h | 0.1 ± 0.05 | 0.1 ± 0.04 | 0.4 ± 0.04 | 0.5 ± 164 | 0.1 ± 0.08 | 0.1 ± 0.05 | 0.1 ± 0.04 | 0.1 ± 0.04 | 0.2 ± 0.09 | 0.2 ± 0.06 | 0.1 ± 0.06 | 0.1 ± 0.04 | 0.2 ± 0.05* | 0.2 ± 0.06* |
| Relative bioavailability 0–8h | 1.0 ± 0.00 | 28.5 ± 91.3* | 49.0 ± 95.5 | 88.0 ± 242 | 171 ± 471 | 1.0 ± 0.00 | 1.1 ± 0.98* | 2.8 ± 2.36* | 794 ± 69.3* | 31.9 ± 21.5 | 1.0 ± 0.00 | 1.1 ± 1.07* | 2.9 ± 2.96* | 72.2 ± 9.87* | 30.6 ± 20.0 |
| Relative bioavailability 0–24h | 10.00 | 28.8 95.4 | 72.3 229 | 141 ± 422 | 170 ± 449 | 1.0 ± 0.00 | 1.1 ± 0.81* | 4.1 ± 4.12* | 530 ± 42.3* | 25.0 ± 16.3 | 1.0 ± 0.00 | 1.1 ± 0.79* | 4.2 ± 4.15* | 49.7 ± 37.8* | 24.2 ± 15.5 |

1 Values are means ± SD, n = 30. Size of data sets are available in Supplemental Table 6. *Statistically significant compared with the reference STE product; † P < 0.05; ‡ P < 0.0001. **Statistically significant compared with the TPG product; † P < 0.05, ‡ P < 0.0001. BDMC, bisdemethoxycurcumin; Cmax, peak plasma concentration; DMC, demethoxycurcumin; HHC, hexahydrocurcumin; NOV, liquid micellar formulation; PHYT, phytosome formulation; STE, standard turmeric extract; TEP, pipeline-curcuminoids combination; THC, tetrahydrocurcumin; Tmax, time to maximum concentration; TPG, Turmipure Gold formulation.

2 Total parent curcuminoids (unconjugated) = curcumin + DMC + BDMC.
3 Curcumin and all its metabolites = curcumin + curcumin sulfate + curcumin glucuronide + THC + THC sulfate + THC glucuronide + HHC + HHC glucuronide + HHC sulfate.

4 Total curcuminoids (parents + reduced and their conjugates) = curcumin + curcumin sulfate + curcumin glucuronide + DMC + DMC sulfate + DMC glucuronide + BDMC + BDMC glucuronide + BDMC sulfate + THC + THC sulfate + THC glucuronide + HHC + HHC glucuronide + HHC sulfate.
in human cells. Similarly, Pal et al. (47) demonstrated that curcumin monoglucuronide and diglucuronide displayed very little antiproliferative activity and had no effect on NF-κB. Even in the case of a lower activity of glucuronide compared with unconjugated curcuminoids, it has been demonstrated that they might become deconjugated in tissues, as shown for other phytochemicals like quercetin and hydroxytyrosol (48, 49). A recent study in mice bone cells by Kunihiro et al. (50) demonstrated that β-glucuronidase can hydrolyze curcumin monoglucuronide and release curcumin to act locally within bones. Oszawa et al. (51) demonstrated that an increase in blood curcumin glucuronide concentration causes an increase in unconjugated curcumin, resulting in the suppression of human colon carcinomas implanted in mice. Taken together, these in vitro data emphasize the fact that all metabolites from curcumin, DMC, and BDMC might contribute to the pharmacological activities of turmeric, and that future studies of turmeric bioavailability and efficacy should not be limited to unconjugated curcumin.

Whereas the molecular structures of curcumin and curcuminoids are responsible for their free radical scavenging activity, other antioxidant and anti-inflammatory properties of curcuminoids have been strongly associated with the regulation of numerous transcription factors, cytokines, protein kinases, adhesion molecules, and redox enzymes that have been linked to aging and pathological conditions. Subsequently, biological efficacy of various turmeric extracts and formulations have shown health benefits in both preclinical and clinical studies, and have been reviewed elsewhere (31, 52–57). As explained earlier, a major limitation of these extracts is their extremely low oral bioavailability, caused by low absorption, rapid metabolism, and rapid excretion following ingestion; often, higher doses or specific formulations are necessary to achieve significant pharmacological effects. This dedicated pharmacokinetic trial demonstrated that the new turmeric colloidal suspension TPG enhanced bioavailability such that 300 mg provided 1.3-fold more plasma curcuminoids than 1500 mg of the standard extract STE (the classical observed efficacy dose). Furthermore, 300 mg of TPG produced 1.5-fold higher curcuminoid plasma concentrations than 1515 mg of the piperine-curcuminoid combination TEP, 2.8-fold higher than 1000 mg of the phytosome formulation PHYT, and the same amount of total curcuminoids in blood as 763 mg of the micellar preparation NOV. The delivery efficacy of the product is therefore not linked only to the amount of curcuminoids contained in the formulation but rather its ability to improve the bioavailability of its components. The biological efficacy of the standard extract STE at 1500 mg had been demonstrated previously (24–31), and 300 mg of the colloidal suspension TPG showed at least equivalent bioavailability, suggesting that fewer capsules would be needed to produce comparable benefits.

Despite numerous discoveries, a limitation of the current study was the number of evaluated outcomes that could increase the risk of type I error, and therefore lead to possible false positives during the statistical analysis. However, the use of the Tukey method adjusting for 10 group comparisons when only 7 comparisons are studied (only STE and TPG compared with all) was quite conservative, and must be highlighted. Another limitation was that some statistical models could not be performed because <15% (45/308) of unconjugated curcuminoid plasma concentrations only were different from zero. In addition, we observed a lot of missing data (minimum n=50%) for the calculation of AUC 0–infinity (data not shown) because it is necessary to have ≥3 values from the time to peak value (Tmax included), and a descendant phase after Tmax.

Table 8: Calculation of the quantity of curcuminoids (and finished products) to be ingested for each formula to reach the same AUC 0–24h as observed after consumption of 300 mg of TPG by healthy human participants (6520 ng·h/mL)^

| Formula | STE | TEP | PHYT | NOV | TPG |
|---------|-----|-----|------|-----|-----|
| Dose-normalized AUC 0–24h of total curcuminoids, ng·h/mL/mg | 3.7 | 3.2 | 13.0 | 136 | 72.9 |
| Quantity of curcuminoids (finished product) to be consumed, mg | 1760 (1920) | 2040 (2260) | 502 (2870) | 48 (763) | 90 (300) |

1NOV, liquid micellar formulation; PHYT, phytosome formulation; STE, standard turmeric extract; TEP, piperine-curcuminoids combination; TPG, Turmipure Gold formulation.
2The dose is calculated using the corresponding dose normalized AUC 0–24h obtained for each product to reach 6520 ng·h/mL, and the quantity of each product is therefore calculated based on the curcuminoids content quantified for each product from (Table 1).
3Here we considered micellar formulation (NOV) dose-normalized AUC to be the same as that obtained at 1000 mg in our study despite the dose obtained from calculation being higher. However, because relative bioavailability is dose dependent (see Discussion), the dose equivalence may be inferior to 2870 mg because relative bioavailability would be higher.
4Here we considered micellar formulation (NOV) dose-normalized AUC to be the same as that obtained at 1000 mg in our study despite the dose obtained from calculation being lower. However, because relative bioavailability is dose dependent (see Discussion), the dose equivalence may be superior to 763 mg because relative bioavailability would be lower.
deliver equivalent pharmacokinetic profiles. Nevertheless, the new colloidal suspension TPG was revealed to be particularly promising in that 300 mg was sufficient to demonstrate bioequivalence to >1500 mg of the standard turmeric extract STE.

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Data Availability
Data described in the manuscript will be made available upon request pending application and approval.

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