The Incorporation of Curcuminoids in Gamma-Cyclodextrins Improves Their Poor Bioaccessibility, Which Is due to Both Their Very Low Incorporation into Mixed Micelles and Their Partial Adsorption on Food

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The Incorporation of Curcuminoids in Gamma-Cyclodextrins Improves Their Poor Bioaccessibility, Which Is due to Both Their Very Low Incorporation into Mixed Micelles and Their Partial Adsorption on Food

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Scope: Turmeric curcuminoids mainly consist of curcumin (CUR), demethoxycurcumin (dCUR), and bisdemethoxycurcumin (bdCUR). CUR displays low bioavailability, partly due to poor solubilization in the intestinal lumen during digestion, while data for dCUR and bdCUR are scarce. The study aims to investigate the bioaccessibility of curcuminoids from turmeric extracts or from gamma-cyclodextrins, considering potential interactions with food.
Methods and results: Using an in vitro digestion model (correlation with CUR bioavailability: $r = 0.99$), the study shows that curcuminoid bioaccessibility from turmeric extract without food is low: bdCUR (11.5 ± 0.6%) > dCUR (1.8 ± 0.1%) > CUR (0.8 ± 0.1%). Curcuminoids incorporated into gamma-cyclodextrins display higher bioaccessibilities (bdCUR: 21.1 ± 1.6%; dCUR: 14.3 ± 0.9%; CUR: 11.9 ± 0.7%). Curcuminoid bioaccessibility is highest without food (turmeric extract: 2.0 ± 0.1%; gamma-cyclodextrins: 12.4 ± 0.8%) and decreases with a meat- and potato-based meal (turmeric extract: 1.1 ± 0.2%; gamma-cyclodextrins: 2.4 ± 0.3%) or a wheat-based meal (turmeric extract: 0.1 ± 0.0%; gamma-cyclodextrins: 0.3 ± 0.1%). Curcuminoids exhibit low (<10%) incorporation efficiencies into synthetic mixed micelles (bdCUR > dCUR > CUR).
Conclusions: bdCUR and dCUR show greater bioaccessibilities versus CUR. Food diminishes curcuminoid bioaccessibility, likely by adsorption mechanisms. Gamma-cyclodextrins improve curcuminoid bioaccessibility.

1. Introduction

Curcuminoids are linear diarylheptanoids found in turmeric, the powdered rhizome of *Curcuma longa*. Turmeric usually contains a mixture of three main curcuminoid species: curcumin (CUR) (60–70%, w/w), demethoxycurcumin (dCUR) (17–27%, w/w), and bisdemethoxycurcumin (bdCUR) (10–18%, w/w) (**Figure 1**).[1,2] These are also usually found in turmeric extracts, albeit at slightly different relative concentrations (CUR: 80.0 ± 1.9%, dCUR: 17.1 ± 1.4%, bdCUR: 2.9 ± 0.6%; mean ± SEM calculated from ref.[2–11]). Turmeric is widely used as a spice, particularly in Asian cuisine, but it has also long been used as a traditional medicine. CUR (the term is actually often inappropriately used in lieu of turmeric) has been the focus of a plethora of studies, including many randomized controlled trials, investigating numerous potential effects against, e.g., inflammation,[12] oxidative stress, cancer,[13] metabolic syndrome,[14] and cognitive function decline/Alzheimer's

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disease.[15] To date, the health benefits of CUR or turmeric are still a matter of great debate.[1,16] The low effectiveness and the heterogeneity of results obtained in clinical trials may partly be explained by the low oral bioavailability exhibited by CUR, which is due to its chemical instability, low solubility, poor gastrointestinal absorption, high metabolism, and rapid systemic elimination.[17] Some studies suggest dCUR and bdCUR could also exert biological effects/health benefits.[18–22] Several clinical trials, whose primary focus was to compare CUR bioavailability from different turmeric formulations, also reported dCUR and bdCUR bioavailabilities,[2–11] which have been suggested by some to be higher than that of CUR.[2,3]

Curcuminoids are lipids (the computed log octanol/water partition coefficients of CUR, dCUR, and bdCUR are around 3.2) and they display poor solubility in the aqueous environment of the gastrointestinal tract. They are assumed to follow the digestive fate of other lipids, i.e., extraction from the food matrix to oil droplets of dietary lipid emulsions followed by incorporation into mixed micelles, which is assumed to be a necessary step for their subsequent absorption by enterocytes.[23] Since bioaccessibility, i.e., for lipid micronutrients the relative fraction retrieved in mixed micelles following digestion, is a limiting factor for the bioavailability of a lipid molecule, including CUR,[9] several studies have investigated in vitro the effect of different formulation strategies on CUR bioaccessibility, e.g. chitosan-coated liposomes,[24] encapsulation using 4-α-glucanotransferase-modified rice starch,[25] or nanoemulsions.[26,27] Although some of the results obtained are fairly encouraging, much remains unknown about the fate of CUR, let alone other curcuminoids, during digestion. Another relevant formulation strategy is the use of cyclodextrins. Cyclodextrins are cyclic oligosaccharides composed of 6–8 glucose monomers linked via α-1,4-glycosidic bonds.[28] They can form complexes with hydrophobic molecules, increasing their stability and solubility. Cyclodextrins are generally recognized as safe (GRAS) and have been used in the pharmaceutical industry but also in the food industry to increase the stability and aqueous solubility of numerous plant bioactives.[28,29] In the case of CUR, one recent study by Flory et al. has shown that its encapsulation into cyclodextrins led to an increase of its bioaccessibility, as compared to several other formulations. They also confirmed their in vitro results in a randomized cross-over trial, showing that the higher bioaccessibility of CUR conferred by gamma-cyclodextrin encapsulation translated into higher bioavailability.[9] Nevertheless, they did not investigate the effect on other curcuminoids, i.e., dCUR and bdCUR, and they did not explore the interaction of food with gamma-cyclodextrins. Additionally, another study in humans has shown that curcuminoids from gamma-cyclodextrins exhibited higher bioavailability compared to those from turmeric, a curcuminoid phytosome formulation, and a formulation consisting of curcuminoids and essential oils of turmeric rhizome.[8]

Hence, we decided to explore the behavior of CUR, dCUR, and bdCUR in the lumen of the upper gastro-intestinal tract by measuring their solubilization efficiencies in the different phases coexisting therein during digestion.[30] To this aim, we first used a static in vitro digestion model to study the solubilization efficiency of curcuminoids in the aqueous and the micellar phases of the digestate. We compared the bioaccessibilities from different formulations, using two turmeric extracts and gamma-cyclodextrins. The use of such a model is particularly relevant for curcumin because it has been shown to predict its relative bioavailability from different formulations very accurately (Pearson's r for in vitro–in vivo correlation = 0.99, $n = 8$; calculated from Flory et al.[9]). We then compared their incorporation efficiencies into synthetic mixed micelles. In vitro studies usually do not consider the effect of food on CUR bioaccessibility, i.e., on its solubilization in the aqueous and/or micellar phases, although humans spend most of their daytime in the postprandial state and CUR can also be added to foods/feeds. Thus, we also decided to assess the effect of different food matrices on curcuminoid in vitro bioaccessibility.

2. Experimental Section

2.1. Chemicals

CUR (99.6% pure), dCUR (98.3% pure), bdCUR (95.9% pure), 2-oleoyl-1-palmitoyl-sn-glycero-3-phosphocholine (phosphatidylcholine, ≥99%), 1-palmitoyl-sn-glycero-3-phosphocholine (lysophosphatidylcholine, ≥99%), free cholesterol (≥99%), oleic acid (reagent grade, ≥99%), 1-monooleoyl-rac-glycerol (monoolein, C18:1,-cis-9), and taurocholic acid sodium salt hydrate (≥95%) were purchased from Sigma–Aldrich (Saint-Quentin-Fallavier, France). Bisphenol B (98.4% pure) was from Interchim (Montluçon, France). Ethyl acetate, acetonitrile, methanol, and chloroform were HPLC grade reagents from Carlo-Erba Reagent (Peypin, France). Acetic acid (LC-MS grade) was from Merck-Millipore (Molsheim, France). Physico-chemical properties of curcuminoids were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/).

2.2. Curcuminoid Formulations

Three curcuminoid formulations were compared in this study. The first one was a dry extract from *Curcuma longa* (71% pure; Sigma-Aldrich), hereafter named common turmeric extract. The second one was a food-grade dry extract from *C. longa* (95.1% pure; Quimdis, Levallois-Perret, France), hereafter named highly pure turmeric extract. The third one was a food-grade gamma-cyclodextrin formulation, prepared as follows: 16% of the highly pure turmeric extract (Quimdis) was mixed at room temperature in a continuous kneader with 62% gamma-cyclodextrin (CAVAMAX W8 FOOD, Wacker Chemie AG, Munich, Germany), 20% water, and 2% butylated hydroxytoluene (98% pure; Métaux et Chimie, Cergy-Pontoise, France). The mixture thus obtained was frozen at −18 °C before colloidal silica (SIPERNAT 2200, Evonik Industries AG, Hanau, Germany) addition (30% silica, 70% mixture) and the final mixture was then ground in a blender.

2.3. In Vitro Digestions

In order to study the bioaccessibility of curcuminoids from the different formulations, a static in vitro digestion model was applied, as previously described.[30] In addition, to compare the

Table 1. Composition of the meals used for the in vitro digestions.

	Meat- and potato-based meal	Wheat-based meal
Ingredients[a)]		
Boiled potatoes	6.7 g	–
Fried minced beef (5% fat)	1.2 g	–
Whole wheat	–	7.5 g
Olive oil	0.2 g	0.075 g
Nutritional composition (g 100 g^{-1} fresh weight)		
Lipids	3.6	3.2
Carbohydrates	13.8	60.9
Proteins	5.3	9.9
Fibers	1.5	10.9
Nutritional composition (energy%)		
Lipids	29.1	8.5
Carbohydrates	49.4	73.0
Proteins	18.8	11.9
Fibers	2.7	6.5

[a)] For boiled potatoes, fried minced beef and olive oil, nutritional composition was obtained from the CIQUAL (Centre d'Information sur la Qualité des Aliments – Information center on food quality) database (https://ciqual.anses.fr/). For whole wheat, nutritional composition was that provided by the manufacturer.

effect of different foods on curcuminoid bioaccessibility, three curcuminoid-rich meals were used, each containing 1 mg CUR, equivalent to 133 ppm when food was present. The first condition had no food. The second condition was a meat- and potato-based meal, to which olive oil was added so that the final lipid content was 3.6% w/w[31] (**Table 1**). These ingredients were chosen to mimic a typical human meal, with a macronutrient composition close to current French nutritional references for adults, i.e., 10–20 energy% proteins, 35–40 energy% lipids, 40–55 energy% carbohydrates. As cereals are staple foods in many animal diets, the third condition was mainly composed of organic wheat bought from a local supermarket, to which olive oil was also added so that the final lipid content was 3.2% w/w (Table 1). A total of 7.5 g of meal were ground in 32 mL of NaCl 0.9% (30 s at 6000 and 22 000 rpm for the meat- and potato-based meal and the wheat-based meal, respectively) (T18 basic Ultra-Turrax disperser, IKA, Staufen, Germany). At the end of the digestion, the aqueous phase containing mixed micelles was separated from food particles by centrifugation (2000 × *g* for 1 h 07 min at 10 °C). In order to eliminate non-micellar particles that were recovered in the aqueous phase, it was passed through a 0.8 and a 0.22 µm filter (mixed cellulose esters; Merck-Millipore) to obtain the micellar phase. The digestate at the end of the duodenal digestion and the different phases obtained after centrifugation, i.e., the aqueous and the micellar phases and the non-solubilized food debris (Figure S1, Supporting Information) were collected, weighed, and samples were stored at −20 °C until lipid extraction and HPLC analysis.

Bioaccessibility is defined as the relative amount of an ingested nutrient that was available for absorption in the gut during digestion. In the case of phytochemicals, there is no consensus on how to separate the bioaccessible aqueous phase from structures not taken up by enterocytes, e.g., larger lipid droplets or crystals.[32] For carotenoids, another lipid phytochemical, a combination of centrifugation and filtration at 0.2 µm is the most widely used method.[33] However, in the case of CUR, its bioaccessibility is often assessed with no filtration step.[24–27,34] In order to compare the results with others and to better characterize the distribution of curcuminoids in the different phases coexisting in the lumen of the small intestine during digestion, curcuminoid bioaccessibility was measured before and after filtration (hereafter named curcuminoid solubilization efficiency in the aqueous and micellar phases, respectively). The solubilization efficiency of a given curcuminoid in the aqueous and micellar phases was calculated as the ratio of the amount of the given curcuminoid found respectively in the aqueous and micellar phases relative to that of the given curcuminoid found in the digestate at the end of the in vitro digestion.

2.4. Synthesis of Mixed Micelles

Mixed micelles were formed as previously described[35,36] to mimic those found in the human duodenum during digestion.[37,38] Briefly, monoolein (0.3 mM), oleic acid (0.5 mM), phosphatidylcholine (0.04 mM), lysophosphatidylcholine (0.16 mM), and cholesterol (0.1 mM) dissolved in trichloromethane/methanol (2:1, v/v) and pure curcuminoids (concentration range: 0.1–20 µM) dissolved in ethanol were transferred to a glass tube, and the solvent mixture was carefully evaporated under nitrogen. The dried residue was dispersed in Tris buffer (Tris–HCl 1 mM, $CaCl_2$ 5 mM, NaCl 100 mM, pH 6.0) containing 5 mM taurocholate and was incubated at room temperature for 1 h. The solution was mixed by sonication in a bath sonicator (Branson 3510 MT, 40 kHz; Branson Ultrasonics, Danbury, CT, USA) for 30 min at 15 °C and then incubated at room temperature for 1 h. It was then filtered through mixed cellulose ester membranes (0.22 µm) (Merck-Millipore). Curcuminoid concentration was measured by HPLC before and after filtration.

2.5. Curcuminoid Extraction

Curcuminoids were extracted from 500 µL samples using a modified method of Schiborr et al.[39] The mixture was extracted twice with two volumes of an ethyl acetate/methanol mixture (95/5; v/v). Bisphenol B solubilized in methanol was used as an internal standard[40] and was added to the samples at the first extraction. The organic phases obtained after centrifugation (1200 × *g*, 10 min, 4 °C) were evaporated to dryness under nitrogen, and the dried extract was solubilized in 200 µL methanol. A volume of 10–50 µL was used for HPLC analysis.

2.6. Curcuminoid Quantification

Curcuminoids were separated and quantified as previously described,[41] using a 5 µm C18 column (250 × 4.6 mm; Zorbax Eclipse XDB-C18; Agilent Technologies, Les Ulis, France) and a guard column (Zorbax Eclipse XDB-C18 12.5 × 4.6 mm, 5 µm; Interchim). The mobile phase was a mixture of 2% acetic acid/acetonitrile (60/40, v/v). Flow rate was 2 mL min^{-1} and the

column was kept at a constant temperature (40 °C). The HPLC system comprised a Thermo Scientific Ultimate 3000 pump, autosampler, column compartment, and diode array detector. Curcuminoids were detected at 425 nm while bisphenol B was detected at 278 nm and they were identified by retention time and spectra (200–600 nm) compared with pure standards. Quantification was performed using Chromeleon software (version 7.2.10 ES) comparing the peak area with standard reference curves.

2.7. Statistics

Data were expressed as means ± SEM or estimated marginal means ± SEM when specified (i.e., for results stemming from repeated measures ANOVA).

Curcuminoid distribution in the digestate was first analyzed by two-way ANOVA, with CUR, dCUR, or bdCUR percentage as the dependent variable, using a full factorial design with formulation and meal as fixed between-subject factors. Since η^2 values for the effect of formulation were close to 1, data were then analyzed by Welch's one-way ANOVA using Games–Howell test as a post hoc test.

In a first approach, differences in curcuminoid bioaccessibilities were analyzed using repeated measures ANOVA, using a full factorial design with formulation (common turmeric extract, highly pure turmeric extract, and gamma-cyclodextrins) and meal (no food, meat- and potato-based meal, and wheat-based meal) as fixed between-subject factors and curcuminoid (CUR, dCUR, and bdCUR) and digestion phase (aqueous and micellar phase) as within-subject factor. Departures from normality were assessed using Q–Q plots of standardized residuals. Mauchly's statistic was calculated for each ANOVA to test for violations of the assumption of sphericity. Mauchly's statistic was significant for all ANOVAs, so all *p*-values were corrected using the Greenhouse–Geisser epsilon. If analyses revealed a significant main effect, pairwise comparisons of the different levels of the main effect were carried out using the Bonferroni correction.

In a second approach, the statistical analysis was simplified by analyzing differences in curcuminoid bioaccessibilities in each digestion phase, i.e., using repeated measures ANOVA, using a full factorial design with formulation and meal as fixed between-subject factors, and curcuminoid as within-subject factor.

Since interaction terms exhibited significant *p*-values, differences in the bioaccessibility of each curcuminoid were then analyzed by two-way ANOVA, using a full factorial design with formulation and meal type as fixed between-subject factors. Departures from normality were assessed using Q–Q plots of standardized residuals. Differences in the bioaccessibility of each curcuminoid for each meal type were further analyzed by one-way ANOVA. Departures from normality were assessed using Q–Q plots of standardized residuals. Homogeneity of variances was tested by Levene's test. Tukey's test was used as a post hoc test for pairwise comparisons while in case of heteroscedasticity, Welch's ANOVA was carried out with Games–Howell test as a post-hoc test.

Values of $p < 0.05$ were considered significant. Statistical analyses were performed using SPSS 28 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Curcuminoid Profiles of the Formulations

The relative quantities of CUR, dCUR, and bdCUR measured in the digestate when the common turmeric extract, the highly pure turmeric extract, or gamma-cyclodextrins were added to in vitro digestions are given in Table S1, Supporting Information. The curcuminoid profiles from the highly pure turmeric extract and gamma-cyclodextrins were not significantly different from one another (CUR: $p = 0.562$; dCUR: $p = 0.640$; bdCUR: $p = 0.803$; Games-Howell test *p*-values following Welch's one-way ANOVA) whereas that from the common turmeric extract differed significantly, with less CUR and more dCUR and bdCUR ($p < 0.001$ for all pairwise comparisons).

3.2. Solubilization Efficiency of Curcuminoids following In Vitro Digestions

Following in vitro digestions, the digestate was centrifuged to separate undigested food debris from the aqueous phase, which was then filtered to obtain the micellar phase (Figure S1, Supporting Information). When all curcuminoids were considered together, i.e., the sum of CUR, dCUR, and bdCUR, solubilization efficiencies in the micellar phase were significantly affected by formulation type (gamma-cyclodextrins > common turmeric extract = highly pure turmeric extract; $p < 0.001$) and meal (no food > meat- and potato-based > wheat-based; $p < 0.001$) (Table S2, Supporting Information). Solubilization efficiencies of curcuminoids in the aqueous phase displayed a profile relatively similar to that observed in the micellar phase, albeit with higher values (estimated marginal mean of curcuminoid bioaccessibility in the aqueous vs micellar phase: 5.8 ± 0.5 vs 2.3 ± 0.4; $p < 0.001$), with only a notable difference for the meal effect (no food = meat- and potato-based > wheat-based; $p < 0.001$) (Table S3, Supporting Information).

Since CUR, dCUR, and bdCUR might exhibit different bioaccessibilities, we then analyzed the effect of formulation type and meal on the solubilization efficiency of each curcuminoid. Indeed, solubilization efficiencies of curcuminoids in the micellar phase differed and ranked as follows: bdCUR > dCUR > CUR ($p < 0.001$), and were significantly affected by formulation (gamma-cyclodextrins > common turmeric extract > highly pure turmeric extract; $p < 0.001$) and meal type (no food > meat- and potato-based > wheat-based; $p < 0.001$) (**Table 2** and Table S2, Supporting Information). In the absence of food, and considering the common turmeric extract, dCUR and bdCUR solubilization efficiencies in the micellar phase were 2.3 and 14.4 times greater than that of CUR. Since in the repeated measures ANOVA, all interaction terms were statistically significant ($p < 0.001$), we further explored the effect of formulation and meal type on the solubilization efficiency of each curcuminoid in the micellar phase (**Figure 2** and Table S2, Supporting Information). The efficiency of CUR solubilization in the micellar phase was significantly affected by formulation type: CUR from gamma-cyclodextrins exhibited a significantly higher solubilization efficiency compared to that from the two turmeric extracts, which were not significantly different from one another (Figure 2A). This difference was seen both in the absence of food (common

Table 2. Effect of meal and formulation type on the efficiency of curcuminoid solubilization in the micellar phase.

	CUR[a)]	dCUR	bdCUR	Marginal mean	*p*-value
Overall	1.9 ± 0.1[a] (n = 36)	2.7 ± 0.1[b] (n = 36)	6.1 ± 0.3[c] (n = 36)	3.6 ± 0.2 (n = 108)	<0.001
Meal type					<0.001
No food	4.5 ± 0.2 (n = 12)	5.8 ± 0.2 (n = 12)	12.5 ± 0.5 (n = 12)	7.6 ± 0.3[a] (n = 36)	
Meat- and potato-based	1.1 ± 0.2 (n = 12)	2.1 ± 0.2 (n = 12)	5.5 ± 0.5 (n = 12)	2.9 ± 0.3[b] (n = 36)	
Wheat-based	0.2 ± 0.2 (n = 12)	0.2 ± 0.2 (n = 12)	0.4 ± 0.5 (n = 12)	0.2 ± 0.3[c] (n = 36)	
Formulation type					<0.001
Common turmeric extract	0.5 ± 0.2 (n = 12)	1.0 ± 0.2 (n = 12)	6.1 ± 0.5 (n = 12)	2.5 ± 0.3[a] (n = 36)	
Highly pure turmeric extract	0.5 ± 0.2 (n = 12)	0.9 ± 0.2 (n = 12)	2.6 ± 0.5 (n = 12)	1.3 ± 0.3[b] (n = 36)	
Gamma-cyclodextrin	4.8 ± 0.2 (n = 12)	6.1 ± 0.2 (n = 12)	9.7 ± 0.5 (n = 12)	6.8 ± 0.3[c] (n = 36)	

bdCUR, bisdemethoxycurcumin; CUR, curcumin; dCUR, demethoxycurcumin. The effect of the meal × formulation interaction was significant ($p < 0.001$). [a)] Values are estimated marginal mean with their standard error and are expressed as % of the quantity of the corresponding curcuminoid recovered in the digestate. [a, b, c]Mean values with unlike superscript letters were significantly different ($p < 0.05$) for a given variable, i.e., curcuminoid species, meal type, and formulation type.

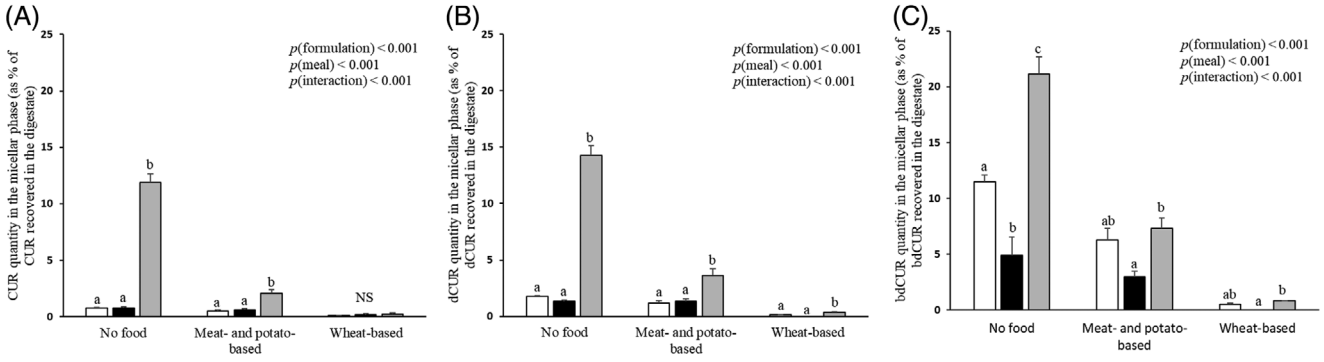

Figure 2. Efficiencies of curcuminoid solubilization in the micellar phase following in vitro digestions. Three curcuminoid-rich meals were compared, each containing 1 mg CUR. The first condition had no food. The second condition was a meat- and potato-based meal, to which olive oil was added so that the final lipid content was 3.6% w/w. The third condition was composed of wheat, to which olive oil was also added so that the final lipid content was 3.2% w/w. A) Solubilization efficiency of CUR. B) Solubilization efficiency of dCUR. C) Solubilization efficiency of bdCUR. White bar: common turmeric extract; black bar: highly pure turmeric extract; grey bar: curcuminoids incorporated into gamma-cyclodextrins. Values are means with their standard errors represented by vertical bars (n = 4). Values with unlike letters were significantly different for a given meal.

turmeric extract: 0.8 ± 0.1; highly pure turmeric extract: 0.8 ± 0.1; gamma-cyclodextrins: 11.9 ± 0.7) and with the meat- and potato-based meal (common turmeric extract: 0.5 ± 0.1; highly pure turmeric extract: 0.6 ± 0.1; gamma-cyclodextrins: 2.1 ± 0.3), as highlighted by the significant interaction between formulation and meal type. CUR solubilization efficiency was also significantly affected by meal type and ranked as follows: no food > meat- and potato-based meal > wheat-based meal (Figure 2A). dCUR solubilization efficiency in the micellar phase displayed a profile similar to that observed for CUR (Figure 2B). bdCUR solubilization efficiency (Figure 2C) was significantly affected by formulation type and ranked as follows: gamma-cyclodextrins = common turmeric extract > highly pure turmeric extract, thereby differing from the results obtained for CUR and dCUR.

Solubilization efficiencies of curcuminoids in the aqueous phase displayed a profile relatively similar to that observed in the micellar phase, with only a notable difference for the meal effect (no food = meat- and potato-based > wheat-based; $p < 0.001$). In the absence of food, and considering the common turmeric extract, dCUR and bdCUR solubilization efficiencies in the aqueous phase were 1.7 and 9.3 times greater than that of CUR (**Table 3** and Table S3, Supporting Information). The effect of formulation and meal type on the solubilization efficiency of each curcuminoid in the aqueous phase are shown in **Figure 3** and Table S3, Supporting Information.

The efficiencies of curcuminoid transfer from the aqueous phase to the micellar phase following in vitro digestions, which correspond to the ratio of the quantity of a given curcuminoid in the micellar phase to its quantity in the aqueous phase, are shown in Table S4, Supporting Information. The efficiencies of curcuminoid transfer differed and ranked as follows: bdCUR > dCUR > CUR ($p < 0.001$), and were significantly affected by formulation (gamma-cyclodextrins > common turmeric extract = highly pure turmeric extract; $p < 0.001$) and meal type (no food > meat- and potato-based > wheat-based; $p < 0.001$).

3.3. Modifications of Curcuminoid Profiles of the Formulations during In Vitro Digestions

Since CUR, dCUR, and bdCUR exhibited significantly different solubilization efficiencies in the aqueous and micellar phases,

Table 3. Effect of meal and formulation type on the efficiency of curcuminoid solubilization in the aqueous phase.

	CUR[a)]	dCUR	bdCUR	Marginal mean	*p*-value
Overall	5.2 ± 0.2^{a} ($n = 36$)	6.0 ± 0.3^{b} ($n = 36$)	11.3 ± 0.4^{c} ($n = 36$)	7.5 ± 0.3 ($n = 108$)	<0.001
Meal type					<0.001
No food	6.4 ± 0.4 ($n = 12$)	8.0 ± 0.5 ($n = 12$)	17.4 ± 0.7 (n =12)	10.6 ± 0.5^{a} ($n = 36$)	
Meat- and potato-based	7.3 ± 0.4 ($n = 12$)	8.3 ± 0.5 ($n = 12$)	13.6 ± 0.7 ($n = 12$)	9.7 ± 0.6^{a} ($n = 36$)	
Wheat-based	1.8 ± 0.4 ($n = 12$)	1.7 ± 0.5 ($n = 12$)	2.9 ± 0.7 ($n = 12$)	2.1 ± 0.5^{b} ($n = 36$)	
Formulation type					<0.001
Common turmeric extract	3.0 ± 0.4 ($n = 12$)	3.8 ± 0.5 ($n = 12$)	13.3 ± 0.7 ($n = 12$)	6.7 ± 0.5^{a} ($n = 36$)	
Highly pure turmeric extract	2.7 ± 0.4 ($n = 12$)	3.2 ± 0.5 ($n = 12$)	5.3 ± 0.7 ($n = 12$)	3.7 ± 0.5^{b} ($n = 36$)	
Gamma-cyclodextrin	9.9 ± 0.4 ($n = 12$)	11.0 ± 0.5 ($n = 12$)	15.2 ± 0.7 ($n = 12$)	12.0 ± 0.5^{c} ($n = 36$)	

bdCUR, bisdemethoxycurcumin; CUR, curcumin; dCUR, demethoxycurcumin. The effect of the meal × formulation interaction was significant ($p < 0.001$). [a)] Values are estimated marginal mean with their standard error and are expressed as % of the quantity of the corresponding curcuminoid recovered in the digestate. [a, b, c] Mean values with unlike superscript letters were significantly different ($p < 0.05$) for a given variable, i.e., curcuminoid species, meal type, and formulation type.

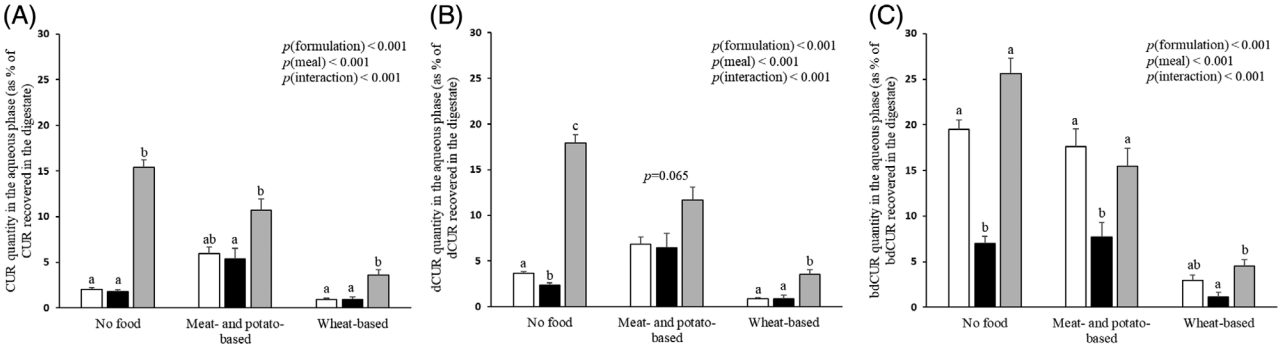

Figure 3. Efficiencies of curcuminoid solubilization in the aqueous phase following in vitro digestions. Three curcuminoid-rich meals were compared, each containing 1 mg CUR. The first condition had no food. The second condition was a meat- and potato-based meal, to which olive oil was added so that the final lipid content was 3.2% w/w. The third condition was composed of wheat, to which olive oil was also added so that the final lipid content was 3.2% (w/w). A) Solubilization efficiency of CUR. B) Solubilization efficiency of dCUR. C) Solubilization efficiency of bdCUR. White bar: common turmeric extract; black bar: highly pure turmeric extract; grey bar: curcuminoids incorporated into gamma-cyclodextrins. Values are means with their standard errors represented by vertical bars ($n = 4$). Values with unlike letters were significantly different for a given meal.

i.e., bdCUR > dCUR > CUR, the curcuminoid distribution profiles in the aqueous and micellar phases when the common turmeric extract, the highly pure turmeric extract, or gamma-cyclodextrins were added to in vitro digestions were modified compared to those observed in the digestate (**Table 4**). Namely, there was overall a significant decrease in %CUR, while %dCUR was only modestly affected and there was a significant increase in %bdCUR. The decrease in %CUR was observed for all conditions, ranking as follows: common turmeric extract > highly pure turmeric extract > gamma-cyclodextrins in the absence of food while there was no significant difference between the highly pure turmeric extract and gamma-cyclodextrins with the meat- and potato-based meal. %dCUR increased with the highly pure turmeric extract and gamma-cyclodextrins while for the common turmeric extract, it decreased in the absence of food and it did not change significantly with the meat- and potato-based meal. For %bdCUR, there was a significant increase for all conditions ranking as follows: common turmeric extract > highly pure turmeric extract > gamma-cyclodextrins in the absence of food while there was no significant difference between the highly pure turmeric extract and gamma-cyclodextrins with the meat- and potato-based meal.

3.4. Competition between Curcuminoids during Digestion

Since dCUR and bdCUR are present in turmeric together with CUR and since they are also found in most CUR formulations, we investigated whether they could compete with CUR for its solubilization during digestion. To this aim, we compared CUR solubilization efficiency, both in the aqueous and micellar phases, when the common turmeric extract or pure CUR were added to in vitro digestions. There was no significant difference in CUR solubilization efficiency between the common turmeric extract and pure curcumin, whether in the micellar phase (estimated marginal means: common turmeric extract, 0.46 ± 0.03; curcumin, 0.51 ± 0.03; $p = 0.306$, and p for interaction with meal = 0.161) (Table S2, Supporting Information) or in the aqueous phase (estimated marginal means: common turmeric extract, 2.97 ± 0.19; curcumin, 2.92 ± 0.20; $p = 0.865$ and p for interaction with meal = 0.670) (Table S3, Supporting Information).

3.5. Incorporation of Pure CUR in Synthetic Mixed Micelles

Pure curcuminoids solubilized in ethanol were mixed at various concentrations, i.e., from 0.1 to 20 μM, with mixed micelle

Table 4. Effect of meal and formulation type on curcuminoid distribution in the different phases obtained from the in vitro digestions.

		No food[a)]			Meat- and potato-based		
		Digestate	Aqueous phase	Micellar phase	Digestate	Aqueous phase	Micellar phase
Common turmeric extract	**%CUR**	74.4 ± 0.1	37.7 ± 0.2	29.1 ± 0.4	75.9 ± 0.4	63.8 ± 0.6	33.6 ± 3.2
	%dCUR	15.7 ± 0.0	14.1 ± 0.0	14.1 ± 0.0	15.8 ± 0.0	15.3 ± 0.1	17.7 ± 0.5
	%bdCUR	9.9 ± 0.1	48.2 ± 0.2	56.7 ± 0.4	8.3 ± 0.5	20.9 ± 0.5	48.7 ± 2.9
Highly pure turmeric extract	**%CUR**	86.0 ± 0.0	78.5 ± 0.8	72.0 ± 2.7	86.1 ± 0.1	83.5 ± 0.2	67.7 ± 2.5
	%dCUR	12.0 ± 0.0	14.3 ± 0.7	17.6 ± 0.9	11.9 ± 0.1	13.7 ± 0.3	23.2 ± 1.5
	%bdCUR	2.0 ± 0.0	7.2 ± 0.2	10.4 ± 3.2	2.0 ± 0.0	2.8 ± 0.1	9.1 ± 1.0
Gamma-cyclodextrin	**%CUR**	85.7 ± 0.0	82.9 ± 0.0	82.4 ± 0.1	86.0 ± 0.1	84.4 ± 0.1	75.6 ± 1.4
	%dCUR	12.2 ± 0.0	13.8 ± 0.1	14.1 ± 0.0	12.1 ± 0.1	12.9 ± 0.0	18.3 ± 0.8
	%bdCUR	2.1 ± 0.0	3.3 ± 0.0	3.5 ± 0.1	1.9 ± 0.0	2.7 ± 0.1	6.1 ± 0.7

bdCUR, bisdemethoxycurcumin; CUR, curcumin; dCUR, demethoxycurcumin. Since the quantity of dCUR or bdCUR was sometimes below our quantification or detection limit following digestions with the wheat-based meal, curcuminoid distribution profiles for this meal are not displayed. [a)] Values are mean ($n = 4$ for each meal × formulation combination) with their standard error and are expressed as % of curcuminoid quantity recovered in the corresponding digestion phase.

Table 5. Incorporation of curcumin in synthetic mixed micelles.

CUR[a)]			dCUR			bdCUR		
Concentration before filtration[b)] [μM]	Concentration after filtration [μM]	Incorporation efficiency [%]	Concentration before filtration [μM]	Concentration after filtration [μM]	Incorporation efficiency [%]	Concentration before filtration [μM]	Concentration after filtration [μM]	Incorporation efficiency [%]
0.02 ± 0.00	<LoD	0%	0.05 ± 0.00	<LoD	0%	0.08 ± 0.00	<LoD	0%
0.09 ± 0.01	<LoD	0%	0.16 ± 0.00	<LoD	0%	0.20 ± 0.00	0.01 ± 0.00	3.9 ± 1.0%
0.33 ± 0.02	<LoD	0%	0.30 ± 0.03	<LoD	0%	0.39 ± 0.01	0.01 ± 0.00	1.7 ± 0.7%
0.62 ± 0.04	<LoD	0%	0.63 ± 0.01	0.01 ± 0.01	1.6 ± 0.8%	0.93 ± 0.02	0.03 ± 0.01	3.7 ± 0.9%
4.63 ± 0.38	0.22 ± 0.02	4.8 ± 1.1%	4.10 ± 0.02	0.12 ± 0.02	3.0 ± 0.6%	4.72 ± 0.22	0.14 ± 0.02	2.9 ± 0.3%
9.60 ± 0.49	0.21 ± 0.02	2.2 ± 0.2%	7.97 ± 0.10	0.33 ± 0.09	4.2 ± 1.1%	8.09 ± 0.15	0.28 ± 0.08	3.5 ± 0.9%
23.92 ± 0.90	2.00 ± 0.09	8.4 ± 0.6%	17.05 ± 0.14	0.79 ± 0.19	4.6 ± 1.2%	17.71 ± 0.64	0.84 ± 0.29	4.8 ± 1.6%

[a)] Values are mean ($n = 3$) with their standard errors; [b)] The curcuminoid concentration of solutions containing mixed micelles components and pure curcuminoids were measured by HPLC before and after filtration of aggregates with a diameter greater than 0.22 μm, leaving a micellar phase.

components, i.e., lipid digestion products, bile lipids, and bile salts. The range of curcuminoid concentrations was chosen based on the concentrations measured in the aqueous or micellar phase following in vitro digestions. Curcuminoid concentration was measured by HPLC before and after filtration of aggregates with a diameter greater than 0.22 μm, leaving a micellar phase. Following filtration, CUR could not be detected at starting concentrations lower or equal to 1 μM while it showed relatively low incorporation efficiencies, i.e., below 10%, at greater starting concentrations (**Table 5**). Following filtration, dCUR and bdCUR could be detected from lower starting concentrations (from 0.63 and 0.20 μM, respectively) but incorporation efficiencies were also low, i.e., below 10%, and not statistically different from that of curcumin.

4. Discussion

The first important observation is that curcuminoid solubilization efficiency in the micellar phase (obtained by centrifugation followed by filtration) was fairly low (2.0%; common turmeric extract in the absence of food). It was also fairly low, albeit higher, i.e., 4%, in the aqueous phase (obtained by centrifugation only). This shows that a large fraction of curcuminoids in the aqueous phase were solubilized in structures with a diameter >220 nm, i.e., much larger than that of mixed micelles. The use of a filtration step is supported by the fact that this filtration cutoff is close to the intestinal mucus pore size[42,43] but in the case of CUR, the bioaccessible phase is obtained most of the time by centrifugation only,[24–27,34] with a notable exception in Flory et al.[9] This probably leads to an overestimation of CUR bioaccessibility (by a factor 2 in our case) since CUR solubilized in larger lipid droplets, bound to macromolecular structures, or CUR crystals,[44] which would not be taken up by enterocytes, are not removed from a non-filtered digestate. In this study, we quantified curcuminoids in both phases since this allows us to better characterize their distribution between the different structures that coexist in the lumen of the small intestine during digestion. Whether considering the aqueous or the micellar phase, curcuminoid solubilization efficiency was low, indicating that most curcuminoids were present in the pellet following centrifugation of the digestate (no

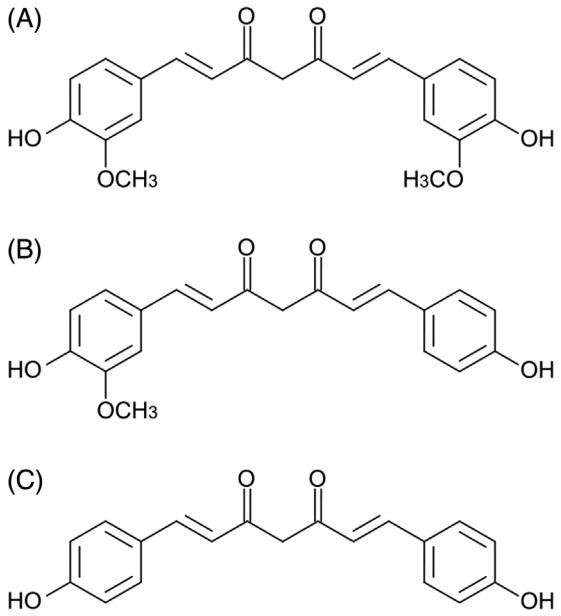

Figure 1. Chemical structures of the three main curcuminoids found in turmeric. A) Curcumin; B) demethoxycurcumin; C) bisdemethoxycurcumin.

floating lipid layer was observed at the end of the digestions). This suggests that curcuminoids remain adsorbed to partially digested food debris and/or other insoluble structures.[30,45]

Another important result is that curcuminoids displayed poor, i.e., <10%, incorporation efficiencies into synthetic mixed micelles whose composition mimics that of mixed micelles found in the human duodenum during digestion.[46] These are low compared to what we have previously shown for several other lipid micronutrients at similar concentrations, i.e., vitamin D (cholecalciferol: 39%, 25-hydroxycholecalciferol: 21%; 1-α-hydroxycholecalciferol: 62%),[35] retinol (95%, unpublished data), and retinyl esters (retinyl acetate: 98%; retinyl propionate: 100%; retinyl palmitate: 100%),[36] vitamin E (tocopherol: 98%; tocopheryl acetate: 98%) (unpublished data and Desmarchelier et al.[30]), or carotenoids (lutein: 89%; beta-carotene: 49%; astaxanthin: 37%).[47] Importantly, this low incorporation efficiency agrees with the low bioaccessibility/bioavailability of non-formulated CUR observed in all studies. This result may be linked to the repartition of the polar groups in curcuminoids: they are located on both phenyl groups and on the heptane connecting them (Figure 1), thereby hindering their insertion into mixed micelles, which are composed of a hydrophobic core and a hydrophilic corona. Since curcuminoid incorporation efficiency in synthetic mixed micelles was four to eight times lower than curcuminoid transfer efficiency from the aqueous to the micellar phase following in vitro digestions with no food, we put forward that curcuminoids found in the micellar phase are mostly solubilized in structures other than mixed micelles, contrarily to what has been previously assumed.[9,24–27,48] It is beyond the scope of this study to identify the structures allowing the solubilization of curcuminoids but candidates include proteins, which curcuminoids can bind with relatively high affinity,[49] unilamellar and multilamellar liposomes, which are vesicle-like vehicles suggested to transport lipids during digestion,[50] or of course the formulation itself, i.e., gamma-cyclodextrins in our case.

Since dCUR and bdCUR have also been suggested to exert health effects[18–21] and since differences in their bioaccessibilities would likely result in differences in their bioavailabilities, it is relevant to compare their solubilization efficiencies with that of CUR. Interestingly, compared to CUR, both dCUR and bdCUR displayed higher solubilization efficiencies in the aqueous (2.3 and 14.4 times higher, respectively) and micellar phase (1.7 and 9.3 times higher, respectively), following digestion of the common turmeric extract in the absence of food. The difference was actually so marked that following digestions containing the common turmeric extract, bdCUR became the major curcuminoid in the aqueous and micellar phases, accounting for approximately 50% of all curcuminoids. When studying the bioaccessibility of CUR, all studies actually measure curcuminoid bioaccessibility,[24–27,48] i.e., they do not differentiate the three curcuminoid species because they do not use analytical separation. As a consequence, they most likely overestimate CUR bioaccessibility, depending on how much dCUR and bdCUR are present in their starting material. In our case, following digestion of turmeric extract in the absence of food, curcuminoid solubilization efficiency in the micellar and aqueous phase was 2.5 and 1.9 times greater than that of CUR, respectively. Of note, Flory et al. did use analytical separation but only reported results for CUR.[9]

Although we did not observe differences in incorporation efficiencies in synthetic mixed micelles between the three curcuminoids at starting concentrations >1 μM, dCUR and bdCUR, which respectively lack 1 and 2 methoxy groups, were more efficiently incorporated at starting concentrations <1 μM. Nevertheless, this might not account for the difference in solubilization efficiencies we measured following in vitro digestions, especially for bdCUR, and we cannot rule out that dCUR and bdCUR are better solubilized than CUR in structures other than mixed micelles. Since dCUR and bdCUR are present in turmeric and derived products and since they exhibit higher bioaccessibilities, we tested whether they could compete with CUR for its solubilization. Importantly, the results of the in vitro digestions containing either pure CUR or the common turmeric extract clearly show that there is no negative effect of dCUR and bdCUR on CUR solubilization efficiency (Tables 2 and 4).

Only few studies compared the bioavailability of the different curcuminoids. A study in mice showed that the bioavailability of curcuminoids ranked as follows: bdCUR > dCUR > CUR,[51] which was also shown in a study in humans measuring the bioavailability of curcuminoids from a standard curcumin extract and a curcumin phosphatidylcholine complex.[7] Another study in humans measured the bioavailability of curcuminoids from a turmeric extract and gamma-cyclodextrins.[8] Unfortunately, the authors did not compare the bioavailability of the different curcuminoids so we calculated them based on average AUC (0–12 h) and curcuminoid dose. Curcuminoid bioavailability ranked as follows: bdCUR > dCUR > CUR (relative bioavailability vs CUR for the turmeric extract: bdCUR, 106.1; dCUR, 12.1; relative bioavailability vs CUR for gamma-cyclodextrins: bdCUR, 4.2; dCUR, 2.5). Therefore, our results regarding curcuminoid relative bioaccessibilities agree with results from studies that compared curcuminoid bioavailability.

Since curcuminoids, more precisely CUR from turmeric, have been shown to display very low bioavailability,[17] partly due to low bioaccessibility and absorption efficiency, we decided to investigate whether formulated curcuminoids would lead to an improvement of their solubilization efficiencies. This is particularly relevant in the case of curcuminoids since it has recently been shown that increasing CUR bioaccessibility is the most successful strategy to improve its oral bioavailability.[9] To this goal, we used three formulations: two turmeric extracts and a gamma-cyclodextrin formulation where CUR is at least partly incorporated into a hydrophobic pocket.[52–54] Our results clearly show that the curcuminoids from the two turmeric extracts displayed similar bioaccessibilities while curcuminoids incorporated into gamma-cyclodextrins exhibited higher bioaccessibilities (respectively 6.2 and 13.8 times greater in the micellar phase in the absence of food as compared to the common and the highly pure turmeric extract, respectively). The increase in curcuminoid bioaccessibility when incorporated in gamma-cyclodextrins was observed for all three curcuminoids and across all food matrices (Figures 2 and 3). Our results agree with those obtained by Flory et al. for CUR in the absence of food (data for dCUR and bdCUR were not provided).[9] Indeed, they reported that CUR solubilization efficiency in the micellar and aqueous phase were respectively 16.1 ± 5.5 and 13.6 ± 2.6 times greater when incorporated into gamma-cyclodextrins as compared to the native extract (vs 14.9 ± 2.1 and 7.3 ± 0.5 in the present study). Our results also agree with results obtained in humans showing a higher acute bioavailability of CUR or curcuminoids incorporated into gamma-cyclodextrins compared to CUR or curcuminoids from turmeric extracts.[8,9] Moreover, long-term (12 weeks) supplementation of curcuminoid incorporated into gamma-cyclodextrins has been shown to increase curcuminoid status, while eliciting no adverse effects, notably through a positive interaction with bile acids leading to an increase of curcuminoid solubility.[55] Additionally, the curcuminoid distribution profiles in the aqueous or micellar phase were less modified with gamma-cyclodextrins than with the common turmeric extract, as also reported in vivo in humans by Purpura et al.[8] At first glance, this could suggest that curcuminoids incorporated into gamma-cyclodextrins mostly remain incorporated during digestion. However, gamma-cyclodextrins have been reported to undergo hydrolysis by alpha-amylases during digestion.[28,56] Our in vitro digestion model provided two alpha-amylases, a bacterial one from the artificial saliva during the oral phase, and a porcine one from the pancreatin added during the intestinal phase, with the latter reported to lead to even faster gamma-cyclodextrin hydrolysis compared to human alpha-amylase.[57] Nonetheless, this degradation has been suggested to be slowed down in the presence of guest molecules[58] and bdCUR has been shown to be able to inhibit human and porcine alpha-amylase[20] while CUR has been suggested to inhibit alpha-amylase in silico.[59] Thus, it seems possible that gamma-cyclodextrins hydrolysis by alpha-amylase was inhibited in the presence of curcuminoids, which could explain that the curcuminoid distribution profiles of gamma-cyclodextrins were less modified compared to those of the turmeric extracts in the absence of food. Hence, the observed increase in the bioaccessibility of curcuminoids from the gamma-cyclodextrin formulation could be due to their association and/or incorporation with gamma-cyclodextrins during a significant part of digestion, limiting their adsorption to partially digested food debris and/or other insoluble structures. Additionally, gamma-cyclodextrins have an outer diameter of 1.75 nm, which explains why the increase in solubilization efficiency was also seen in the micellar phase, i.e., following filtration at 220 nm.[28,56]

Finally, we investigated the effect of food on curcuminoid bioaccessibility. Indeed, curcuminoids or curcuminoid formulations could interact with co-ingested foods or feeds, which could result in lower curcuminoid bioavailability. We observed a very strong negative interaction between food and curcuminoid bioaccessibility. The foods added, mimicking a human, and an animal meal, provided many molecules and it is not possible to know which ones affected curcuminoid bioaccessibility. Nevertheless, dietary fibers can have a negative impact on lipid phytochemical bioaccessibility,[60,61] which could explain why curcuminoid bioaccessibility was minimal with the wheat-based meal (which had 7.3 times more fibers than the meat- and potato-based meal). Moreover, cereal-based meals have been shown to inhibit lipolysis during digestion[62,63] and undigested food debris have been shown to be able to trap some lipids during digestion, such as vitamin E.[30] Interestingly, the decrease in curcuminoid solubilization efficiency upon food addition was stronger for the gamma-cyclodextrin formulation. Since, as suggested by our results, curcuminoids mostly remain incorporated into gamma-cyclodextrins during digestion, this suggests that gamma-cyclodextrins remain to some extent adsorbed to partially digested food debris and/or other insoluble structures. Since food is present most of the day in the gastrointestinal tract,[64] such differences could lead to practical recommendations concerning intake timing, i.e., at fast versus with a meal, and the nature of the foods co-consumed. Unfortunately, most studies investigating the bioaccessibility of CUR from formulations do not add any food to their model.[9,24–27,48] For example, Flory et al. recommend the intake of a dose of CUR with each principal meal in order to build up steady-state plasma CUR concentrations, although they did not assess the effect of food, whether in vitro or in their clinical trial.[9] However, a few studies investigated the interaction of curcuminoids with co-ingested foods[65] or with the structure and composition of the source matrix,[2] showing effects on curcuminoid bioavailability in formulation- and food-specific fashions. We thus recommend considering the almost certain, and probably very variable, effects of foods on curcuminoid bioaccessibility, by using experimental conditions which mimic as closely as possible the conditions under which the formulations will be ingested, i.e., on an empty stomach or during meals whose average food composition is reproduced in the experimental model.

We acknowledge some limitations for the present study. Some are inherent to the use of a static in vitro digestion model, which of course does not capture the complexity of the digestive tract, e.g., dynamics of digestive secretions and food intakes, or curcuminoid interactions with the gut microbiota.[66] Another limitation is the fact we used turmeric, which provides all three major curcuminoids at different doses, and not the pure compounds at equal doses to compare their bioaccessibilities. Although it allows us to mimic what happens with most turmeric formulations, an inverse dose-bioaccessibility relationship cannot be completely excluded. However, it is important to note

that our results are in agreement with other in vitro[9] or in vivo studies.[7–9]

To conclude, we here show that curcuminoid bioaccessibility during in vitro digestion is low, with most curcuminoids remaining adsorbed to partially digested food debris and/or other insoluble structures. This is partly due to their poor intrinsic incorporation efficiency into mixed micelles. Furthermore, we show that the three main naturally-occurring curcuminoids display fairly different behaviors, with CUR exhibiting the lowest bioaccessibility. Importantly, a gamma-cyclodextrin formulation, where curcuminoids are at least partly incorporated into a hydrophobic pocket, yielded the highest bioaccessibilities, for all three curcuminoids and across all foods tested. This is probably because curcuminoids remained mostly associated with gamma-cyclodextrins during digestion. This also likely explains the higher bioavailabilities in humans of curcuminoids incorporated into gamma-cyclodextrins compared to curcuminoids from turmeric extracts.[8,9] Finally, curcuminoid bioaccessibility during digestion, regardless of the formulation, was highly influenced by the presence of food, stressing the relevance of not assessing the bioaccessibility/bioavailability of new curcuminoid formulations only in the fasted state.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

P.B., F.H., L.L., G.M., G.G., and C.D. declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. C.R. works for ID4Feed, which commercializes and conducts research on feed supplements for farm animals based on plants and plant extracts.

Author Contributions

P.B., C.R., and C.D., funding acquisition; F.H., L.L., G.M., G.G., and C.D., investigation; P.B. and C.D., methodology; P.B. and C.D., project administration; P.B., C.R., and C.D., resources; C.D., supervision; P.B. and C.D., validation; C.D., visualization; writing - original draft, CD; writing - review & editing, all authors.

Data Availability Statement

Data described in the manuscript shall be made available upon request to the corresponding author.

Keywords

bioavailability, bisdemethoxycurcumin, curcumin, demethoxycurcumin, digestion, food matrix, phytochemicals, polyphenols, turmeric

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