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Pharmacokinetic studies of commercially available curcumin formulations in healthy humans: A systematic comparison with novel highly bioavailable curcuRouge® formulation

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ABSTRACT

Curcumin has been widely studied for its therapeutic potential, but its clinical efficacy is limited by poor bioavailability. Various strategies have been developed to enhance curcumin absorption.

This systematic review evaluated the pharmacokinetic performance of commercially available absorption-enhanced curcumin formulations by comparing their AUC_{0-t} and C_{max} values, normalized per milligram of curcumin, against unformulated standard extracts.

Among the formulations analyzed, curcuRouge®, an amorphous curcumin formulation, demonstrated the highest absorption (AUC_{0-t}: 17.23 ng/mL·h) and peak concentration (C_{max}: 5.47 ng/mL), significantly outperforming others ($P < 0.05$). CurQfen® (9.86 ng/mL·h) and NovaSol® (10.91 ng/mL·h) showed similar but lower absorption than curcuRouge®. Relative to unformulated curcumin, curcuRouge® showed a 162.7-fold increase in bioavailability, making it approximately 1.7 and 1.6 times more bioavailable than NovaSol® and CurQfen®, respectively. In terms of C_{max}, curcuRouge® was 182.0-fold higher than NovaSol® (96.5-fold) and CurQfen® (116.5-fold), indicating it is 1.9 and 1.6 times more absorbable, respectively.

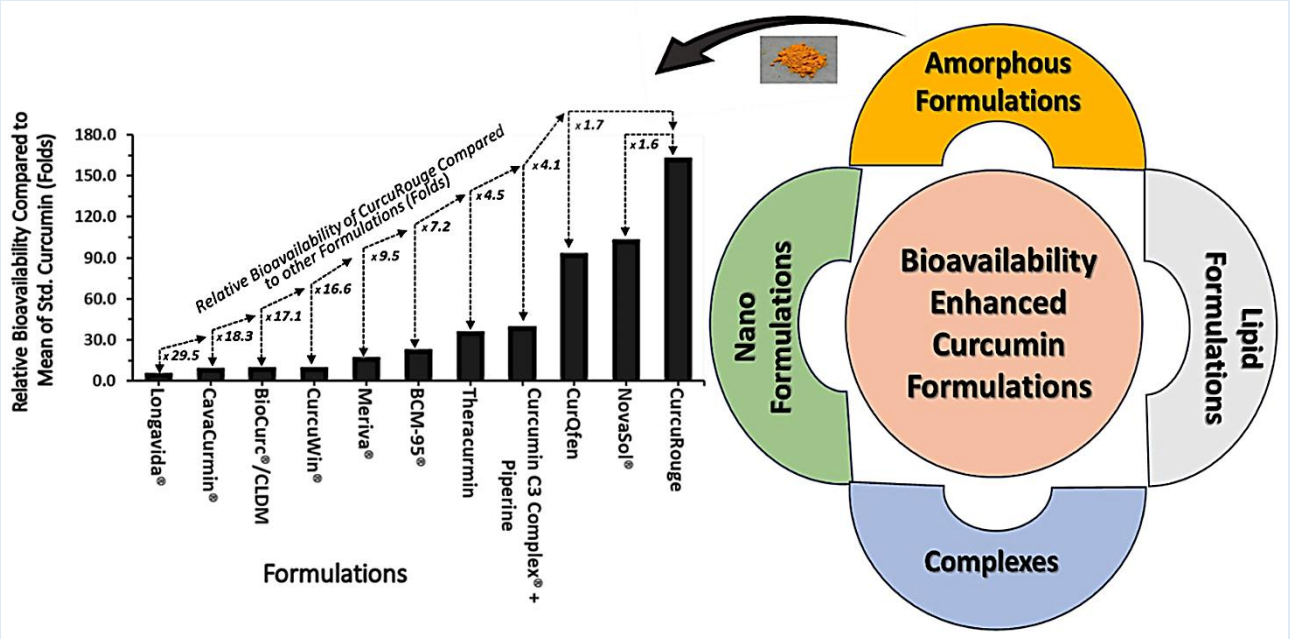
These findings suggest that curcuRouge® represents a significant advancement in curcumin delivery with its

amorphous structure and enhanced dissolution rate. This analysis offers a robust comparative framework for evaluating bioavailability in commercial curcumin formulations and highlights curcuRouge® as a promising option for improved therapeutic efficacy.

Highlights:

1. Curcumin's therapeutic use is limited due to poor bioavailability.
2. Study compares the pharmacokinetics of absorption-enhanced curcumin formulations.
3. Amorphous structure promotes curcuRouge® stability, solubility and absorption efficiency.
4. curcuRouge® showed excellent bioavailability than other curcumin formulations at modest doses.

Keywords: curcumin; Curcuminoids; amorphous; curcuRouge®, human, pharmacokinetics, bioavailability.



Graphical Abstract: Pharmacokinetic studies of commercially available curcumin formulations in healthy humans: A systematic comparison with novel highly bioavailable curcuRouge® formulation

INTRODUCTION

Interest in natural health remedies, anti-inflammatory agents, and antioxidant compounds continues to grow, particularly with the expanding applications of curcumin in dietary supplements, pharmaceuticals, functional beverages, personal care products, skincare, and cosmetics. Global market trends indicate that the curcumin industry is projected to increase from USD 680 million in 2025 to USD 1.7 billion by 2035, reflecting a compound annual growth rate (CAGR) of 9.7% [1].

Curcumin, the principal lipophilic polyphenol in the rhizome of *Turmeric (Curcuma longa L.)*, is the major curcuminoid responsible for turmeric's characteristic yellow pigment and biological activity [2]. It is also used as a flavoring agent, dietary supplement, and in traditional therapeutic medicine [3,4]. Due to its hydrophobic nature (*logP* 3.2), curcumin is significantly more soluble in organic solvents than in aqueous media [5–7]. Curcumin has received extensive scientific attention owing to its diverse therapeutic applications in traditional systems of medicine such as Ayurveda, Unani, Siddha, Chinese, and Arabic medicine [8,9]. It possesses a broad spectrum of pharmacological properties, including antioxidant [10], anti-inflammatory [11 - 13], antimicrobial [14], anticancer [15 - 17], neuroprotective [18], nephroprotective [19], cardioprotective, hypoglycemic [20], immunomodulatory [21], and hepatoprotective effects [22,23]. Furthermore, curcumin has been associated with improvements in cognitive function and memory [24], as well as the management of stress [25], anxiety [26, 27], chronic diseases [15, 28], and metabolic disorders [29, 30]. At the molecular level, it modulates multiple targets, influencing enzyme expression, cell-cycle regulation, signaling proteins, receptors, cytokines, prostaglandin biosynthesis, and cell adhesion molecules [31].

Despite its broad pharmacological potential and favorable safety profile, the clinical utility of curcumin remains limited due to poor oral bioavailability. Although stable under gastric conditions, orally administered curcumin results in low plasma and tissue concentrations because of poor aqueous solubility, limited intestinal absorption, and rapid systemic elimination [32]. Consequently, substantial research has focused on developing novel delivery systems to improve solubility, stability, absorption, and metabolic resistance, ultimately enhancing therapeutic outcomes. Numerous formulation strategies have been explored, including nanocrystals, nanocomposites, nanosuspensions, polymeric nanoparticles and micelles, liposomes, solid lipid nanoparticles (SLNs), emulsions, nanoemulsions, self-assemblies, hydrogels, nanogels, cyclodextrin inclusion complexes, phospholipid complexes (phytosomes), and bioenhancer systems [7, 32-36]. Although many of these formulations are still under investigation, several have progressed to commercial availability. Both preclinical and clinical studies consistently demonstrate improved bioavailability, enhanced therapeutic efficacy, and excellent safety across diverse curcumin formulations [32,34,37-39]. However, claims of enhanced bioavailability must be interpreted cautiously. Reported data often vary because some studies measure curcumin alone, while others include total curcuminoids. Moreover, inconsistencies in study design, ethnicity of participants, analytical methodologies, sampling protocols, and formulation characteristics complicate inter-study comparisons. As a result, there is no consensus on the optimal dosage or formulation required to achieve therapeutic plasma concentrations, given the limited intestinal absorption of curcumin and its analogs. To address these discrepancies, recent comparative investigations have evaluated commercial curcumin formulations standardized by curcumin content per milligram, rather than by total curcuminoids. This

normalization is critical, as supplement manufacturers often make generalized claims of superior absorption or faster onset, which may mislead consumers without specialized scientific understanding.

Among the formulations evaluated, curcuRouge®, containing amorphous curcumin, demonstrated markedly improved dissolution and gastrointestinal absorption compared with conventional crystalline forms. Pharmacokinetic studies showed rapid increases in plasma total curcumin (free plus conjugated), reaching peak concentrations within one hour, followed by first-order elimination kinetics and nearly complete intestinal uptake within eight hours [40]. This enhanced absorption suggests greater systemic availability of unconjugated curcumin, considered the pharmacologically active form. Nevertheless, emerging evidence indicates that curcumin conjugates may also exhibit biological activity. Proposed that curcumin conjugates, such as glucuronides, can undergo enzymatic deconjugation by β-glucuronidase, releasing free curcumin at target sites [41]. Therefore, the distinction between active and inactive forms remains under debate. Fanca-Berthon et al (2021) further recommended that future studies should not focus exclusively on unconjugated curcumin, as conjugated metabolites may contribute to its pharmacodynamic effects [42].

Given curcumin's multifunctional therapeutic potential, the advancement of scientifically validated formulation technologies offers significant promise for its application in medicine, nutrition, and functional food systems. However, the lack of standardized comparative data across formulations underscores the need for comprehensive, well-controlled pharmacokinetic evaluations to establish the most effective, safe, and cost-efficient approaches for enhancing curcumin bioavailability. The present comprehensive review consolidates clinical pharmacokinetic evidence for commercially available curcumin formulations with enhanced absorption. It provides an updated overview of formulation strategies that successfully improve curcumin bioavailability in humans. Although curcumin's therapeutic efficacy is well documented, realizing its full clinical potential depends on the development of transparent, reproducible, and scientifically validated delivery systems that optimize bioavailability without overstating efficacy claims.

Search strategy and methodology: To capture a wider spectrum of relevant publications, a comprehensive literature search was conducted across Scopus, PubMed/MEDLINE, Web of Science, Google Scholar, and the Cochrane Library from inception to August 31, 2025 (Figure 1). No filters or restrictions on language, geography, publication date, or indexing were applied to ensure inclusivity. Search terms included *curcumin, curcuma, curcuminoids, turmeric extract, curcumin clinical trials, clinical studies, curcumin pharmacokinetics, human intervention, bioavailable curcumin,* and *bioavailability of curcumin.* Boolean operators (AND, OR) and truncation enhanced search sensitivity and algorithms. Only full-text studies were included for accurate data extraction and analysis. Abstracts were screened, and only pharmacokinetic studies in healthy human volunteers were selected for final assessment and reference lists of included studies were manually examined for additional relevant data. In vitro, animal,

preclinical, in-silico, case reports, and meta-analyses were excluded. The review compares commercially available bioavailability-enhanced curcumin formulations with the curcuRouge® formulation.

Selected curcumin formulations for data extraction: Data extracted from eligible studies on commercial curcumin formulations included brand and manufacturer details, product type, formulation composition, clinical study design, participant number and ethnicity, first author, publication year, and references (Table 1). Supplementary Table S1 summarizes dose information from human pharmacokinetic studies, detailing the material dose, total curcuminoids, curcumin per capsule, and the actual administered dose. Dosages of unformulated curcumin extract used as reference controls are also included. This dataset enables accurate comparison of formulation composition, dosage, and pharmacokinetic outcomes across studies, supporting evaluation of bioavailability among different commercial curcumin products.

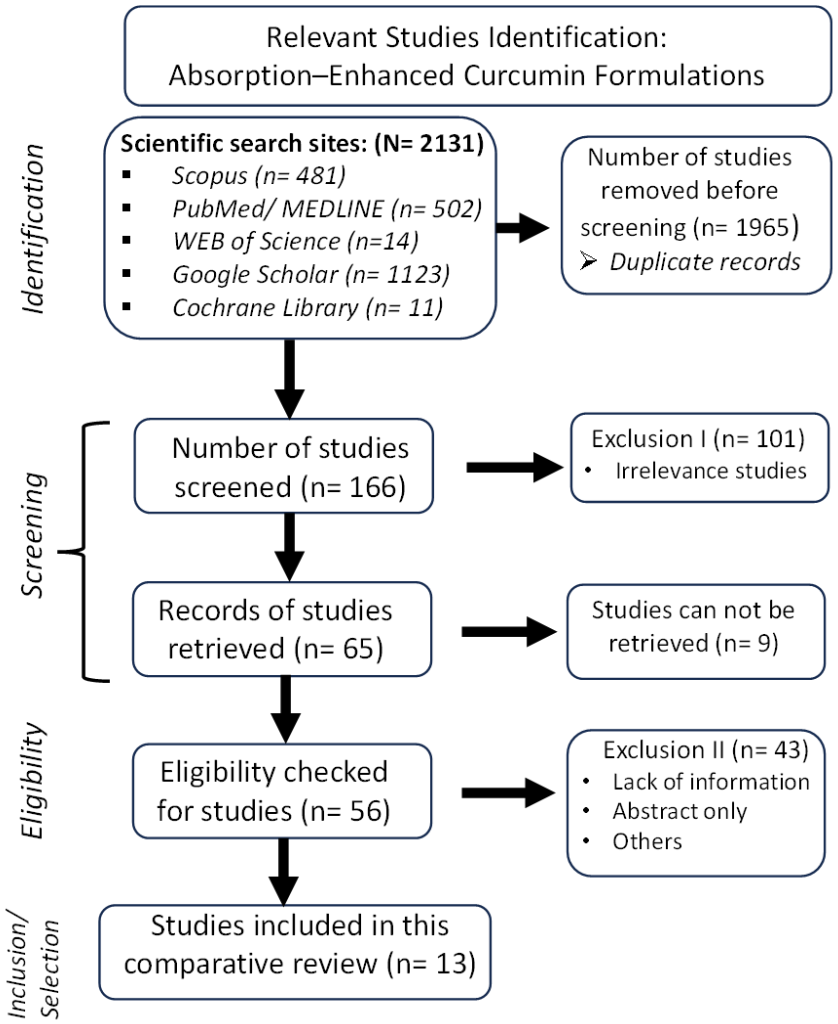


Figure 1. Schematic illustration of the flow chart of relevant studies identified for absorption-enhanced curcumin formulations included in the comparative analysis.

Table 1. Compositional description of commercially available curcumin formulations, and their clinical study information on human bioavailability.

Curcumin Formulation	Description	Composition	Study design	Participants number & ethnicity	Refs
Biocurcumax™ BCM-95® (Arjuna Natural Extracts Ltd., India)	Curcumin complex with essential oils of turmeric rhizome	86% curcuminoids (65% curcumin) and 5–7% turmeric essential oils; starch, sugars, protein, vitamin C, resin	Crossover	11 Asian (Indian)	Antony et al. (2008)
			Double-blind, crossover	9 Asian (Japanese)	Sunagawa et al. (2015)
			Randomized, double-blind, crossover	11 Caucasian 1 Afro-American	Jager et al. (2014)
			Randomized, double-blind, crossover	11 Caucasian 1 Afro-American	Purpura et al. (2018)
Meriva® (Indena SpA, Italy)	Curcumin is complexed with soy lecithin-derived phosphatidylcholine	20 %curcuminoids to phosphatidylcholine in a 1: 2 weight ratios (Phytosome); leucine, calcium citrate laurate, silicon dioxide, microcrystalline cellulose	Randomized, double-blind, crossover	9 Caucasian	Cuomo et al. (2011)
			Randomized, double-blind, crossover	9 Caucasian	Cuomo et al. (2011)
			Double-blind, crossover	9 Asian (Japanese)	Sunagawa et al. (2015)
			Randomized, open-labeled, crossover	30 Caucasian	Fanca-Berthon et al. (2021)
			Randomized, double-blind, crossover	11 Caucasian 1 Afro-American	Jager et al. (2014)
			Randomized, double-blind, crossover	11 Caucasian 1 Afro-American	Purpura et al. (2018)
Theracurmin™ (Theravalues Corp., Japan)	Curcumin dispersed in colloidal nanoparticles (sub-micron)	Gum ghatti, dextrin, maltose, citric acid, cornstarch, silicon dioxide, calcium stearate, hydroxypropyl methylcellulose, curcumin extract (Curcumin: 10 w/w%, curcuminoids: 2 w/w%) {homogenized at high pressure}	Double-blind, crossover	9 Asian (Japanese)	Sunagawa et al. (2015)
			Randomized	14 Asian (Japanese)	Sasaki et al. (2011)

Curcumin Formulation	Description	Composition	Study design	Participants number & ethnicity	Refs
			Double-blind, crossover	9 Asian (Japanese)	Sunagawa et al. (2021)
Longvida® (Verdure Science, USA)	Curcumin in solid lipid formulation with soy lecithin (encapsulated curcumin within a lipid matrix)	Curcumin: 20-30 %; vegetable derived stearic acid dextrin, hydroxypropyl methylcellulose, ascorbyl palmitate, silicon dioxide, soy lecithin	Randomized, double-blind, crossover	6 Asian (Indian)	Gota et al. (2010)
CurcuWin® (OmniActice Health Technology, India)	Ultra-micronized, water-dispersible curcumin formulation	20-28 % curcumin extract; 63-75% polyvinyl pyrrolidine, cellulosic derivatives, natural oxidants	Randomized, double-blind, crossover	11 Caucasian 1 Afro-American	Jager et al. (2014)
BioCruc®/CLDM (Boston BioPharm, USA)	Curcumin formulation involving liquid droplet micro- micellar	76 mg curcuminoids (64.6 mg curcumin), lauryl macrogol-32 glycerides, polysorbate-20, DL-α-tocopherol, hydroxypropyl cellulose	Randomized, double-blind, crossover	12 Caucasian	Stohs et al. (2018)
NovaSol® (Frutarom, Isreal)	A micelle formulation of curcumin involving polysorbate-80	7% curcumin extract (82% curcumin, 18% curcuminoids); 93 % polysorbate-80 (Tween 80); vegetable glycerin, gelatin	Randomized, double-blind, crossover	23 Caucasian	Schiborr et al. (2014)
			Randomized, open-labeled, crossover		Fanca-Berthon et al. (2021)
CavaCurmin® (Wacker Chemie AG, Germany)	Curcumin in complex with γ-cyclodextrin (CAVAMAX® W8)	61.9 mg curcuminoids (58 mg curcumin), microcrystalline cellulose, g-cyclodextrin	Randomized, double-blind, crossover	11 Caucasian 1 Afro-American	Purpura et al. (2018)
CurQfen™ (Spiceuticals, Akay Group, India)	Curcumin formulation with fenugreek dietary fiber as curcumagalacto-mannosides (CGM)	39.1% curcuminoids (30.7% curcumin), fenugreek dietary fiber	Randomized, double-blind, crossover	8 Asian (Indian)	Kumar et al. (2016)
			Randomized, double-blind, crossover	8 Asian (Indian)	Kumar et al. (2016)
Curcumin C3 Complex® + Piperine (Sabinsa, USA)	Cucuminoids and Bioperine formulation	Pure curcumin powder C3 complex combined with 20 mg of pure piperine powder	Randomized, crossover	10 Asian (Indian)	Shoba et al. (1998)
curcuRouge™ (Therabiopharma Inc., Japan)	Amorphous formulation of curcumin	Corn starch, modified starch, curcumin content/ capsule: 37.3 w/w%, calcium stearate	Double-blind, crossover	12 Asian (Japanese)	Sunagawa et al. (2021)

Data abstraction and comprehensive comparison strategy: A review of the eligible studies revealed substantial discrepancies due to variations in study design, participant ethnicity, sample analysis protocols, sampling times, and formulation administration duration. Single-dose pharmacokinetic experiments typically measured peak plasma concentration (C_{max}), time to reach peak concentration (T_{max}), and area under the concentration-time curve (AUC_{0-t}), which reflects the extent of absorption. Among these, AUC_{0-t} is the most reliable measure of bioavailability, capturing the overall response over time, and is commonly used to assess relative bioavailability (RB) compared to a reference product. Some studies compared curcumin formulations to standard unformulated curcuminoid combinations, while others compared them with commercial absorption-enhanced products (*i.e.,* the competitor's products). In many cases, unconjugated curcumin was undetectable in plasma after oral administration of standard curcumin extract, preventing accurate estimation of AUC_{0-t} or relative bioavailability. Conversely, some approaches tended to overestimate relative bioavailability versus standard or competitor formulations.

Table 2 summarizes pharmacokinetic parameters of standard curcumin extracts used as references (control) across studies of commercially available absorption-enhanced formulations, with dosages ranging from 30 to 1800 mg. Direct comparison of T_{max}, AUC_{0-t}, and C_{max} across formulations is challenging due to the nonlinear relationship between dose and absorption, influenced by first-pass metabolism saturation. To enable systematic comparison, pharmacokinetic parameters of standard unformulated curcuminoid mixtures were normalized per milligram of curcumin from administered doses used in eligible studies. Comparing these mean values with the bioavailability profiles of absorption-enhanced formulations allows estimation of dosages required to achieve comparable systemic exposure and bioequivalence.

Statistical analyses included non-parametric Mann-Whitney tests to compare rankings between two independent curcumin formulations and Chi-square tests for independent pharmacokinetic data, with respective regression models applied to validate findings. This approach provides a robust framework to assess dose-dependent absorption and the relative bioavailability of commercially available curcumin formulations.

Results analysis: Meriva®, a curcumin-phosphatidylcholine phytosome complex formulation, has been reported to increase the relative bioavailability (based on AUC_0–t measurement) of curcumin by 19.2-fold and total curcuminoid absorption by 29.0-fold in a randomized, double-blind, crossover study in humans [43]. However, the pharmacokinetic parameters of Meriva® cannot be directly compared to those reported in independent studies by Jager et al. (2014) [44] (RB: 12.7-fold for curcumin), Purpura et al. (2018) [45] (RB: 9.0-fold for curcumin), and Fanca-Berthone et al. (2021) [42] (5.5-fold for curcumin including conjugates) due to significant differences in study design (see Table 1 and Table S1). Similarly, pharmacokinetic data from a study using Biocurcumax (BCM-95®), a proprietary extract of curcuminoids plus turmeric essential oil, revealed that its relative bioavailability was approximately 6.9-fold greater compared to unformulated standard curcumin extract [46]. In contrast, human pharmacokinetic results for BCM-95® reported by Jager et al (2014) [44] and Purpura et al (2018) [45] were markedly different (RB: 2.6-fold and 1.7-fold, respectively).

In a human pharmacokinetic study, Theracurmin®, a sub-micron colloidal dispersion of curcumin, achieved ~16-fold greater relative bioavailability than unformulated curcumin extract [47]. Longvida®,

curcumin encapsulated in a lipid matrix (SLCP™), demonstrated nearly 100-fold improved relative bioavailability in a human study [48]. CurcuWin®, a water-dispersible curcumin formulation, showed a 136-fold higher relative bioavailability than unformulated curcumin extract in a randomized, double-blind, crossover pharmacokinetic study [44], while NovaSol®, a patented micellar formulation of curcumin, exhibited nearly 185-fold enhancement in relative bioavailability [49]. Cavacurmin®, a cyclodextrin-based curcumin formulation, achieved an 85-fold increase in relative bioavailability in a randomized, double-blind, crossover human study [45]. CurQfen®, a curcumin-galactomannan complex, displayed ~45.5-fold improvement in free curcuminoid bioavailability compared to unformulated curcumin extract, showing a dose-dependent effect [50]. In another randomized, crossover pharmacokinetic study in healthy humans, curcumin C_3 complex administered with piperine showed a 20-fold improvement in relative bioavailability than unformulated curcumin extract [51]. BioCruc®, a liquid droplet micellar formulation of curcumin (CLDM), reported exceptionally high relative bioavailability— ~522-fold greater than unformulated curcumin extract [52]. Sunagawa et al (2015) and Sunagawa et al (2021) [38,40] did not include a control group and instead compared results to other absorption-enhanced curcumin formulations; thus, relative bioavailability could not be determined (Table S1, supplementary information).

The area under the curve ($AUC_{0–t}$), C_{max}, and T_{max} reported for curcumin formulations in eligible studies, along with the estimated curcumin content based on administered dosages, are displayed in Table 2. Units of pharmacokinetic parameters were harmonized for accurate comparisons: $AUC_{0–t}$ and C_{max} are expressed in ng/mL·h and ng/mL, respectively. Values reported in nmol/L·h and nmol/L were converted to ng/mL·h and ng/mL for AUC_{0-t} and C_{max}, respectively, by dividing using a conversion factor of 2.717, based on curcumin's molecular weight (368.38 g/mol). Units reported in ng/g were converted to ng/mL by multiplying using an approximate curcumin density of 1.28 g/mL. Pharmacokinetic values ($AUC_{0–t}$ and C_{max}) were normalized per milligram of curcumin ingested, and relative bioavailability was estimated using mean normalized values of unformulated curcumin extract (see Table 2).

Table 3 summarizes these comparisons for selected absorption-enhanced curcumin formulations. All curcumin formulations significantly enhanced $AUC_{0–t}$ and C_{max} compared to the unformulated extract. However, unformulated curcumin extract $AUC_{0–t}$ varied widely across studies from 3.3 to 446.8 ng/mL·h (~135-fold range of difference), and C_{max} ranged from 1.2 to 144.9 ng/mL (~118-fold range of difference). T_{max} varied from 0.5 to 12 hours. Bioavailability-enhanced formulations exhibited $AUC_{0–t}$ ranging 95.3– 6650.4 ng/mL·h (~69.8-fold range of difference), with variable effects on T_{max}. Relative bioavailability significantly varied across curcumin formulations.

To facilitate direct pharmacokinetic comparisons, some studies normalized C_{max} and $AUC_{0–t}$ to per milligram of curcumin but failed to differentiate between total curcuminoid and curcumin doses, and their comparison was based on the relative bioavailability estimated using the pharmacokinetic parameters of unformulated curcumin extract (as a reference) from an individual study. In the present report, the simplified comparison is based on C_{max}/mg curcumin and $AUC_{0–t}$/mg curcumin administered from formulated curcumin products, compared to the mean values of unformulated curcumin extract across studies. Normalized data are displayed in Table 2, with estimated mean ± SD values of $AUC_{0–t}$ (0.106 ± 0.120 ng/mL·h) and C_{max} (0.030 ± 0.038 ng/mL) (see box plots presented in Figure S1; supplementary information).

Table 2. Summary of pharmacokinetic results from standard curcumin extracts served as a reference material (control) in human bioavailability clinical studies on commercially available curcumin formulations.

Curcumin Formulation	References	Control (Std. Curcumin Extract)					Normalized to per mg Curcumin	
		Curcumin dose in study (mg)	Sampling duration (0-t); h	AUC_{0-t} (ng/mL. h)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t}/ mg Curcumin (ng/mL. h)	C_{max}/ mg Curcumin (ng/mL)
Biocurcumax™BCM-95® (Arjuna Natural Extracts Ltd., India)	Antony et al. (2008)	1436.0	0-8	446.8	144.9	2.0	0.311	0.101
Meriva® (Indena SpA, Italy)	Cuomo et al. (2011)	1295.0	0-24	122.5	9	6.9	0.095	0.007
	Fanca-Berthon et al. (2021)	1140.0	0-24	64.4	21.5	2.7	0.056	0.019
Theracurmin™ (Theravalues Corp., Japan)	Sasaki et al. (2011)	30.0	0-6	4.1	1.8	6	0.137	0.060
CurcuWin® (OmniActice Health Technology, India)	Jager et al. (2014)	1346.8	0-12	10.8	2.3	7.4	0.008	0.002
Longvida® (Verdure Science, USA)	Gota et al. (2010)	NE	0-6	NE	NE	NE		
BioCruc®/CLDM (Boston BioPharm, USA)	Stohs et al. (2018)	323.0	0-8	4.16	1.22	8.6	0.013	0.004
NovaSol® (Frutarom, Isreal)	Schiborr et al. (2014)	410.0	0-24	24.1	2.6	7.5	0.059	0.006
CavaCurmin® (Wacker Chemie AG, Germany)	Purpura et al. (2018)	1774.2	0-12	19.7	2.3	12	0.011	0.001
CurQfen™ (Spiceuticals, Akay Group, India)	Kumar et al. (2016)	321.1	0-12	41.0	11.0	0.5	0.128	0.034
	Kumar et al. (2016)	80.5	0-12	27.8	7.5	0.5	0.346	0.093
Curcumin C3 Complex® + Piperine (Sabinsa, USA)	Shoba et al. (1998)	1582.8	0-3	3.3	5.0	1	0.002	0.003
curcuRouge® (Thera Biopharma Inc., Japan)	Sunagawa et al. (2021)	NE	0-8	NE	NE	NE		
Mean ± Std. Deviation		**885.4 ± 653.1**		**Mean ± Std. Deviation**			**0.106 ± 0.120**	**0.030 ± 0.038**

NE not estimated; curcumin content was calculated from total curcuminoid content in the administered dose in each human clinical study (see details in Table S2)

Table 3 shows that curcuRouge® exhibited the highest absorption and bioavailability ($AUC_{0–t}$/mg curcumin 17.23 ng/mL·h), followed by NovaSol® (10.91 ng/mL·h) and CurQfen® (9.86 ng/mL·h), and were significantly lower than curcuRouge® ($P < 0.05$). Theracurmin® (3.80 ng/mL·h) and curcumin C_3 complex plus piperine (4.20 ng/mL·h) had moderate bioavailability, significantly lower than curcuRouge® ($P < 0.01$), and lower than NovaSol® and CurQfen® ($P < 0.05$). Other formulations exhibited extremely low absorption ($P < 0.001$). C_{max}/mg curcumin values reflected the same trend (Figures 2a and 2b; Table 3). Relative bioavailability analysis (based on the mean values of unformulated curcumin extract across studies) confirmed that curcuRouge® had the highest relative bioavailability $AUC_{0–t}$/mg curcumin (~162.7-fold) and C_{max}/mg curcumin (~182.0-fold), exceeding NovaSol® (102.9-fold and 96.5-fold) and CurQfen® (93.0-fold and 116.5-fold) and outperforming Theracurmin® (35.9-fold and 42.3-fold) and curcumin C_3 complex plus piperine (39.7-fold and 3.2-fold). These results indicate that curcuRouge® is approximately 1.7- and 1.6-times more bioavailable than the NovaSol® and CurQfen®, respectively, and nearly a factor of over 1.9- and 1.6 times more readily absorbable than NovaSol® and CurQfen®, respectively. While curcuRouge® outperformed Theracurmin® and curcumin C_3 complex plus piperine by 4.5-fold and 4.1-fold, respectively, in terms of relative bioavailability $AUC_{0–t}$/mg curcumin, it had a 4.3-times greater relative C_{max}/mg curcumin than that of Theracurmin® and 57.8-times higher than the curcumin C_3 complex plus piperine, indicating a questionably slow absorbability of the curcumin C_3 complex plus piperine formulation. BCM-95® and Meriva® showed relative bioavailability $AUC_{0–t}$/mg curcumin 22.5-fold and 17.1-fold, and relative C_{max}/mg curcumin 11.3-fold and 5.6-fold, respectively, which were 7.2- and 9.5-times lower than curcuRouge® in terms of relative bioavailability $AUC_{0–t}$/mg curcumin. The relative C_{max}/mg curcumin of the curcuRouge® was 16.1-times greater than BCM-95®; however, it was 32.3-times greater than Meriva®, confirming the superiority of the curcuRouge®. Surprisingly, CurcuWin®, BioCruc®, Cavacurmin®, and Longvida® had the lowest relative bioavailability $AUC_{0–t}$/mg curcumin when compared to curcuRouge® (Table 3, Figures 3a and 3b).

T_{max} can indicate absorption rate, but it is influenced by absorption and clearance rates of curcumin, not the extent of absorption [53]. While T_{max} is easier to interpret, the C_{max}/AUC_{0-t} ratio is more precise and is statistically easier to handle. Absorption-enhanced curcumin formulations had a lower mean $C_{max}/AUC_{0–t}$ ratio (0.25 ± 0.19) than the unformulated extract (0.36 ± 0.40). However, the mean T_{max} differed significantly (1.85 ± 1.01 h vs. 5.01 ± 3.87 h, $P < 0.05$). Figure S2 displays data as representative boxplots. The plots of $C_{max}/AUC_{0–t}$ and T_{max} across curcumin dose (Figures 4a & 4b) showed similar correlation profiles, with less scatter for $C_{max}/AUC_{0–t}$, indicating better precision for absorption rate assessment. BCM-95® and Meriva® showed low $C_{max}/AUC_{0–t}$ ratios despite larger T_{max}, whereas curcuRouge®, NovaSol®, Cavacurmin®, and CurQfen® reached C_{max} with higher onset speed (*i.e.,* T_{max}) were consistent with Theracurmin® and Longvida® but with moderate onset speed. CurcuWin® and curcumin C_3 complex plus piperine showed lower $C_{max}/ AUC_{0–t}$ ratio relative to their reported T_{max}, while BioCruc® showed exceptionally high $C_{max}/AUC_{0–t}$ ratio relative to their reported T_{max}. Overall, curcuRouge® achieved a superior absorption rate relative to its T_{max}, despite Cavacurmin® being administered at 3.9 times higher dose, yet exhibited 18.3-fold lower relative bioavailability than curcuRouge®. (see Figure 4c).

Table 3. A systematic comparison of pharmacokinetic profiles normalized to per milligram of curcumin for commercially available curcumin formulations, with relative bioavailability estimated using the calculated mean value for standard curcumin extract (normalized to per milligram of curcumin), along with relative bioavailability of curcuRouge® compared to various absorption-enhanced curcumin formulations.

Curcumin Formulation	References	Formulations Bioavailability (Pharmacokinetics)					Normalized to per mg Curcumin		†Relative Bioavailability Compared to Calculated Mean Value of Std. Curcumin Extract (see Table 2) (Number of Folds)		‡Relative Bioavailability of CurcuRouge™ Compared to various Formulations (Number of Folds)	
		Curcumin dose in study (mg)	Sampling duration (0-t); h	AUC_{0-t} (ng/mL. h)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t}/mg Curcumin (ng/mL. h)	C_{max}/mg Curcumin (ng/mL)	AUC_{0-t}	C_{max}	AUC_{0-t}	C_{max}
Biocurcumax™; BCM-95® (Arjuna Natural Extracts Ltd., India)	Antony et al. (2008)	1300.0	0-8	3096.8	442.0	3.4	2.382	0.340	22.49	11.32	7.2	16.1
	Sunagawa et al. (2015)	279.3	0-6	66	45	4	0.236	0.161	2.23	5.36	72.9	33.9
	Jager et al. (2014)	297.0	0-12	5.8	0.5	3.2	0.020	0.002	0.18	0.06	882.5	3247.8
	Purpura et al. (2018)	355.2	0-12	6.7	0.9	6	0.019	0.003	0.18	0.08	913.6	2157.9
Meriva® (Indena SpA, Italy)	Cuomo et al. (2011)	297.0	0-24	538	50.3	3.8	1.811	0.169	17.10	5.64	9.5	32.3
	Cuomo et al. (2011)	165.0	0-24	272.6	24.2	4.2	1.652	0.147	15.59	4.88	10.4	37.3
	Sunagawa et al. (2015)	152.5	0-6	123.8	58.8	2	0.812	0.386	7.66	12.84	21.2	14.2
	Fanca-Berthon et al. (2021)	146.0	0-24	44.2	13.4	4.8	0.303	0.092	2.86	3.06	56.9	59.6
	Jager et al. (2014)	297.0	0-12	28.7	2.8	1.7	0.097	0.009	0.91	0.31	178.3	580.0
	Purpura et al. (2018)	354.0	0-12	35.1	4.7	1 0	0.099	0.013	0.94	0.44	173.8	411.8
Theracurmin™ (Theravalues Corp., Japan)	Sunagawa et al. (2015)	182.4	0-6	693	231.5	2	3.799	1.269	35.86	42.25	4.5	4.3
	Sasaki et al. (2011)	30.0	0-6	113	29.5	1	3.767	0.983	35.55	32.73	4.6	5.6
	Sunagawa et al. (2021)	90.0	0-8	457.5	91.3	0.5	5.083	1.014	47.98	33.76	3.4	5.4
Longvida® (Verdure Science, USA)	Gota et al. (2010)	163.0	0-inf	95.3	22.4	2.4	0.585	0.137	5.52	4.58	29.5	39.8

Curcumin Formulation	References	Formulations Bioavailability (Pharmacokinetics)					Normalized to per mg Curcumin		†Relative Bioavailability Compared to Calculated Mean Value of Std. Curcumin Extract (see Table 2)		‡Relative Bioavailability of CurcuRouge™ Compared to various Formulations	
		Curcumin dose in study (mg)	Sampling duration (0-t); h	AUC_{0-t} (ng/mL. h)	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t}/mg Curcumin (ng/mL. h)	C_{max}/mg Curcumin (ng/mL)	(Number of Folds)		(Number of Folds)	
									AUC_{0-t}	C_{max}	AUC_{0-t}	C_{max}
CurcuWin® (OmniActice Health Technology, India)	Jager et al. (2014)	297.0	0-12	307.6	27.3	1.4	1.036	0.092	9.78	3.06	16.6	59.5
BioCruc®/CLDM (Boston BioPharm, USA)	Stohs et al. (2018)	387.6	0-8	391.5	282	1.5	1.010	0.728	9.53	24.22	17.1	7.5
NovaSol® (Frutarom, Isreal)	Schiborr et al. (2014)	410.0	0-24	4471.0	1188.1	1.1	10.905	2.898	102.93	96.46	1.6	1.9
	Fanca-Berthon et al. (2021)	50.2	0-24	27.8	10.3	3	0.554	0.205	5.23	6.83	31.1	26.6
CavaCurmin® (Wacker Chemie AG, Germany)	Purpura et al. (2018)	348.0	0-12	327.7	73.2	1	0.942	0.210	8.89	7.00	18.3	26.0
CurQfen™ (Spiceuticals, Akay Group, India)	Kumar et al. (2016)	307.0	0-12	1785.5	345.5	1	5.816	1.125	54.90	37.46	3.0	4.9
	Kumar et al. (2016)	76.7	0-12	756.0	268.4	1	9.857	3.499	93.04	116.49	1.7	1.6
Curcumin C_3 Complex® + Piperine (Sabinsa, USA)	Shoba et al. (1998)	1582.8	0-3	6650.4	149.6	0.75	4.202	0.095	39.66	3.15	4.1	57.8
curcuRouge® (Therabiopharma Inc., Japan)	Sunagawa et al. (2021)	90.0	0-8	1551.0	492.1	2	17.233	5.468	**162.66**	**182.01**		

†*The calculated mean AUC_{0-t}/ mg curcumin of the std. Curcumin extract = 0.106 ng/L. h, and the mean C_{max}/ mg Curcumin of Std. Curcumin Extract = 0.030 ng/L) (Table 2) were used to estimate the relative bioavailability (RB) of the reported commercially available curcumin formulations.* ‡ *Relative bioavailability of curcuRouge® compared to the various commercially available curcumin formulations (curcuRouge® showed the highest ever bioavailability among the so far curcumin formulations reported in the literature).* ***Mean dose 332.94 ± 370.43 (SD)***

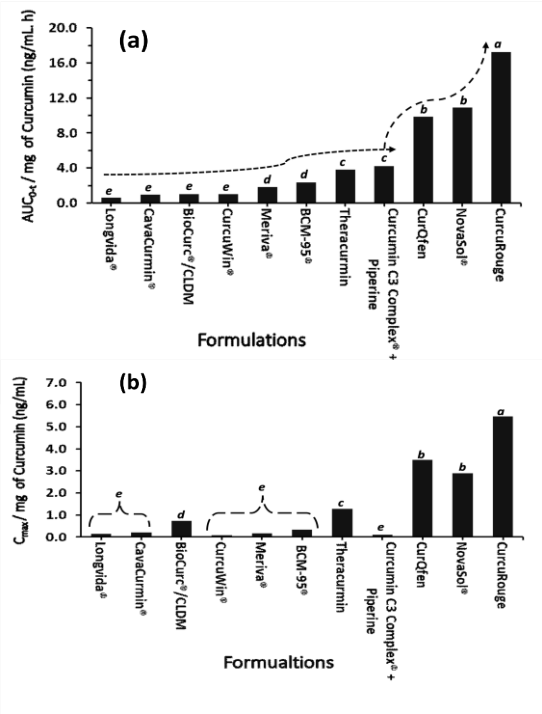


Figure 2. Comparative bar graphs of (a) $AUC_{0\text{-}t}$/mg curcumin, and (b) C_{max}/mg curcumin of commercially available absorption-enhanced curcumin formulations included in the present comparative analysis, demonstrating significant statistical differences from the curcuRouge® formulation. (*Keys illustration*: Different letters on top of each bar indicate a significant difference from others, while bars with similar letters showed no significance: ab, bc & bd (P< 0.05); ac, ad, be (P< 0.01), and ae (P< 0.001).

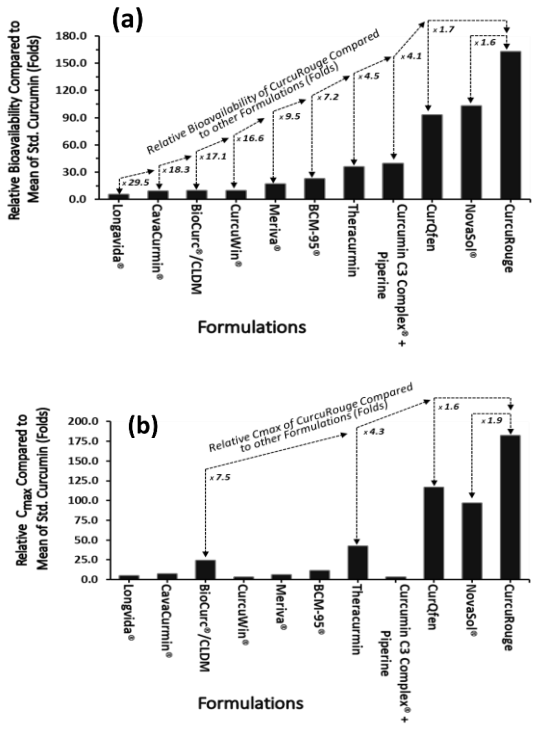


Figure 3. Comparative analysis of (a) relative bioavailability {RB} based on the $AUC_{0\text{-}t}$/mg curcumin and (b) relative C_{max} based on the C_{max}/mg curcumin of commercially available absorption-enhanced curcumin formulations. The values were estimated using the estimated mean values $AUC_{0\text{-}t}$/mg curcumin and C_{max}/mg curcumin of standard curcumin extracts. Also, curcuRouge® formulation showed a several-fold increase in relative bioavailability and C_{max} compared with absorption-enhanced curcumin formulations. (*Keys illustration:* Corresponding arrow and values reflect the number of folds increased in relative bioavailability and C_{max} of absorption-enhanced curcumin formulations when compared to the curcuRouge® formulation.

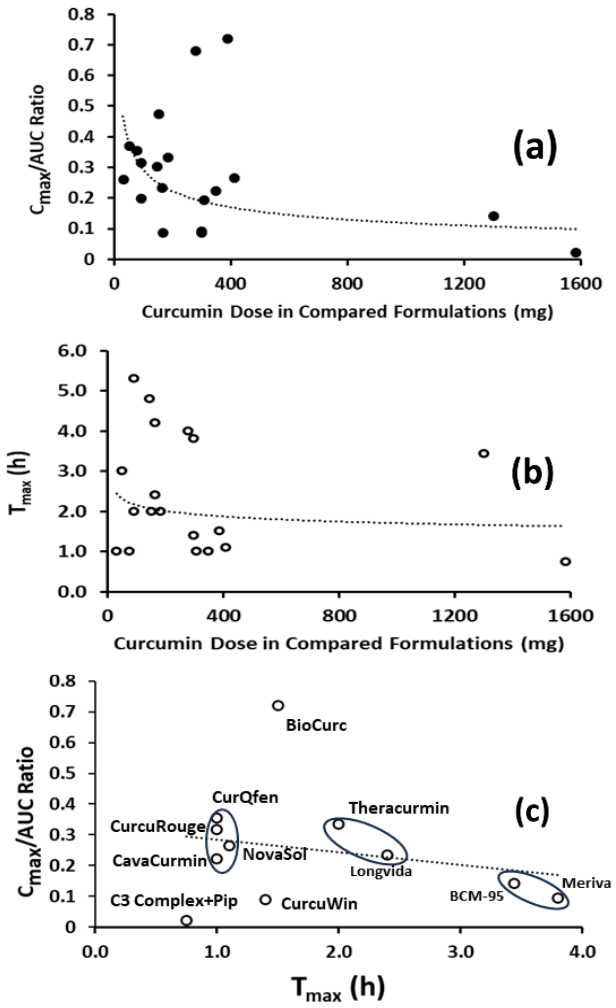


Figure 4. Correlation between (a) C_{max}/AUC_{0-t} ratio normalized per milligram of curcumin, (b) T_{max}, versus curcumin dosage in commercially available absorption-enhanced curcumin formulations, and (c) cross-relationship between C_{max}/AUC_{0-t} ratio normalized per milligram of curcumin versus T_{max} showing the mapping of diverse absorption-enhanced curcumin formulations for absorption rate comparison.

DISCUSSION

Curcumin's limited oral bioavailability mainly arises from its poor water solubility, posing a major challenge for effective formulation and in vivo performance. Numerous strategies have been proposed to overcome this limitation [54]. To evaluate progress, we analyzed and compared absorption-enhanced commercial curcumin formulations using available human pharmacokinetic data. Considerable variation in pharmacokinetic parameters (AUC_{0-t}, C_{max}, and T_{max}) across studies of unformulated curcumin extracts likely results from differences in design and protocols, analytical procedures, dosages, and administration methods. Consequently, comparisons across studies remain limited by this heterogeneity. Among the various strategies to improve curcumin's solubility and dissolution rate, disrupting its crystal lattice to form an amorphous structure appears especially effective. Amorphization enhances aqueous solubility and, therefore, oral bioavailability. A representative product is curcuRouge®, an amorphous curcumin formulation developed to improve solubility, mucoadhesion, and permeation. This nutraceutical transforms crystalline curcumin into an amorphous form stabilized with modified corn starch, which provides moderate mucoadhesive properties through hydrogen bonding

between its functional groups and mucin.

X-ray diffraction confirmed the conversion from crystalline to amorphous curcumin, showing a broad halo typical of amorphous materials and indicating complete amorphization (Figure 5; referred to as the amorphization process). Because of its intrinsically stabilized amorphous form, curcuRouge® can provide a controlled, adjustable release profile by increasing dissolution rate. The formulation employs an amorphous solid dispersion technique, in which amorphous curcumin is dispersed in a high-glass-transition-temperature (*Tg*) matrix. This enhances intermolecular forces, reduces molecular mobility, and stabilizes the amorphous state [55]. Differential scanning calorimetry revealed a single *Tg* peak at 74.4 °C, indicating a single-phase amorphous system and confirming that nucleation and crystal growth were fully inhibited during controlled cooling (see Figure 5). A hydrophobic matrix further limits moisture absorption during processing and curcuRouge® storage, thereby preventing phase separation and recrystallization of amorphous solids. Since higher Tg values generally correspond to greater physical stability [56], amorphous curcumin in curcuRouge® can maintain a higher concentration of active curcumin over time. This stabilization strategy suggests that curcuRouge® can be safely administered at various dosages without toxic or adverse effects, while achieving improved bioavailability compared to crystalline curcumin. Some minor degradation of curcumin may occur during amorphization, likely through cleavage of the β-diketone bond, yielding low-molecular-weight hydrophilic phenolic compounds such as ferulic acid, feruloyl methane, and vanillic acid, which may partially volatilize during processing of the curcuRouge® formulation. Nevertheless, the amorphous formulation's enhanced solubility and stability make curcuRouge® a promising platform for more effective curcumin delivery.

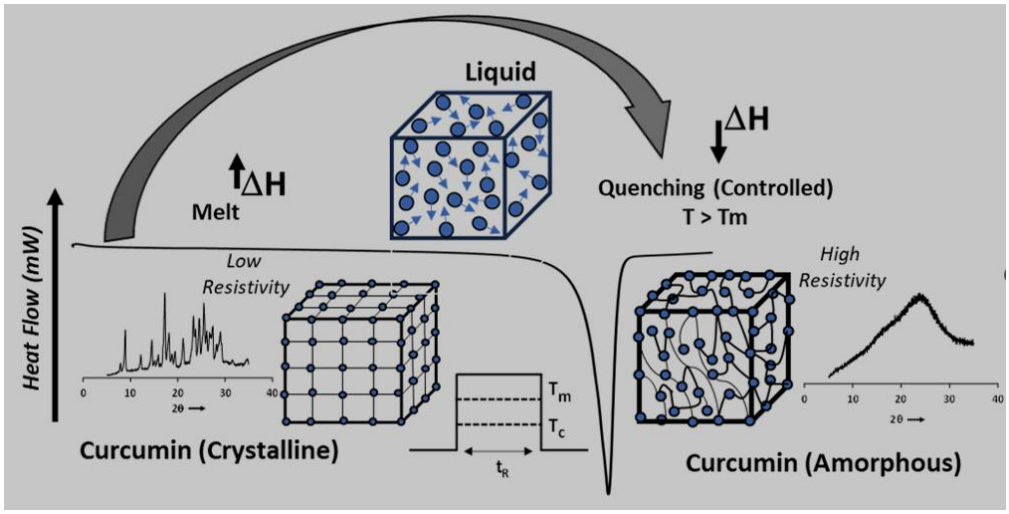


Figure 5. A Schematic of the curcumin amorphization process for the curcuRouge® formulations evaluated in the comparative analysis.

Following oral administration, most curcuminoids are excreted unmetabolized through feces, while the absorbed fraction undergoes sequential metabolic transformations. Initially, curcumin is reduced in the liver and intestinal mucosa to di-, tetra, hexa-, and octa-hydro metabolites (phase I metabolites) [42,57]. It then undergoes extensive phase II metabolism in the gastrointestinal tract, where β-glucuronidase catalyzes conjugation with sulfate and glucuronic acid to form predominantly physiologically inert sulfate and glucuronide conjugates [21,30,58]. Curcuminoids may also experience both reduction and conjugation within hepatic and intestinal microbial environments [43,44,47,49]. Recently, attention has shifted toward the

relative bioavailability of free (unconjugated) curcuminoids and their metabolites due to their superior bioactivity and permeability compared to conjugated forms [59]. Plasma-free curcumin, considered the bioactive fraction, is regarded as the best indicator of bioavailability and possibly bioequivalence [34, 52]. In vivo activity may also involve de-conjugation of curcumin conjugates at specific target sites, liberating the active unconjugated curcuminoids [60]. However, even high oral doses (10–12 g/day) of standard curcumin extract fail to significantly raise plasma concentrations of free curcuminoids [61]. Therefore, developing absorption-enhanced formulations capable of elevating plasma levels of unconjugated curcuminoids remains essential for realizing curcumin's full therapeutic potential.

Both C_{max} (maximum plasma concentration) and AUC_{0-t} (area under the plasma concentration–time curve) depend on the extent of absorption and are expected to correlate closely. The C_{max}/AUC_{0-t} ratio may thus serve as a more robust metric than C_{max} alone for comparing formulations, even if the formulations are not truly bioequivalents, especially those with variable pharmacokinetics. The C_{max}/AUC_{0-t} ratio is less influenced by intrasubject variability and better reflects differences between absorption and disposition rates [53,62]. In absorption-enhanced curcumin formulations, C_{max} may be nonlinearly related to absorption rate, encompassing both absorption and elimination processes, which reduces its kinetic sensitivity. Because curcumin formulations typically exhibit short elimination half-lives, the C_{max}/AUC_{0-t} ratio may provide the most accurate indicator of primary absorption rate. Moreover, integrating the pharmacokinetic relationship between T_{max} (time to reach C_{max}) and the C_{max}/AUC_{0-t} ratio allows for estimation of a theoretical bioequivalence range, offering deeper insight into absorption dynamics [63].

To address bioavailability limitations, the collective bio-enhancement strategy has been applied in curcumin formulations. Comparative evaluation using normalized pharmacokinetic parameters (AUC_{0-t} /mg curcumin and C_{max}/mg curcumin) relative to unformulated curcumin extract effectively reduces inter-study variability, enabling more accurate assessment. Among commercially available formulations, curcuRouge® demonstrated markedly higher AUC_{0-t} values than Theracurmin®, NovaSol®, CurQfen®, and Meriva® in human studies, indicating faster absorption and greater systemic exposure. When efficiency per milligram of curcumin is prioritized—achieving higher exposure with smaller doses—curcuRouge® again outperforms other enhanced formulations. It also exhibits exceptionally high C_{max} values at low doses, combined with a moderately fast T_{max}, greatly surpassing both control and competing curcumin formulations. Physically, curcuRouge® consists of non-uniform particles (~10 µm) that display excellent solubility and dispersibility, while standard curcumin extracts show strong aggregation in aqueous media. Collectively, these attributes underscore curcuRouge®'s superior bioavailability, efficient absorption, and promising potential as an optimized curcumin delivery system.

CurcuWin®, BioCurc®, CavaCurmin®, and Longvida® demonstrated improved systemic exposure over standard curcumin extract, offering faster absorption but moderate evaluation accuracy due to inconsistent dose normalization per milligram of curcumin. Consequently, these formulations lag behind curcuRouge®, Theracurmin®, NovaSoL®, and CurQfen® in pharmacokinetic performance. Although BCM-95® and Curcumin C_3 Complex® plus piperine have shown enhanced bioavailability and clinical efficacy, their absolute pharmacokinetic metrics per milligram remain inconsistent, suggesting better suitability only for higher-dose regimens. Micelle-based NovaSol® formulation avoided phase separation in the gastrointestinal tract, delivering maximal curcumin to the intestinal wall, while CurcuWin® and Longvida® suggested that strategies increasing accessible surface area can promote

absorption and improve bioavailability.

Among the compared formulations, curcuRouge® achieved the highest peak plasma concentration (C_{max}) per milligram of curcumin, coupled with rapid absorption (T_{max}) and strong overall exposure (AUC_{0-t}). These attributes position curcuRouge® as a leading candidate for superior clinical effectiveness. Its enhanced bioavailability may result from enzymatic hydrolysis of conjugated curcumin, increasing the release of free curcumin—the physiologically active form responsible for therapeutic benefits. Consequently, curcuRouge® likely provides better gastrointestinal absorption and higher plasma levels of unconjugated curcumin compared to other absorption-enhanced products. The curcuRouge® composition comprises GRAS (Generally Recognized as Safe) ingredients, ensuring suitability for use in both dietary supplements and functional foods. When choosing among absorption-enhanced curcumin formulations, consumers should consider therapeutic outcomes, dosage convenience, and safety profiles. Overall, curcuRouge® offers an optimal balance of high absorption, rapid onset, safety, and a clean-label composition suitable for multiple dosage forms, supported by clinical evidence of efficacy in improving inflammatory biomarkers.

Limitations and recommendations: Each absorption-enhanced curcumin formulation has limitations. Meriva® uses soy-derived phospholipids that may trigger allergies and delivers less free curcumin due to its phospholipid matrix. BCM-95® shows moderate bioavailability without distinguishing free and metabolized curcumin. Longvida® offers modest curcumin per dose and variable results across studies. Theracurmin® provides moderate bioavailability versus top-tier micellar (NovaSol®) or colloidal (CurcuWin®) forms. Curcumin C_3 Complex® with piperine raises safety and excretion concerns. NovaSol® relies on synthetic surfactants, while curcuRouge® is promising but lacks extensive long-term clinical data. Moreover, most comparative studies omit curcumin metabolite profiling, limiting understanding of pharmacokinetic–pharmacodynamic relationships.

CONCLUSION

Various delivery strategies have been developed to overcome poor oral bioavailability of curcumin, including lipid-based formulations, polymeric nanoparticles and micelles, phospholipid complexes, cyclodextrin inclusion complexes, and co-administration with bioenhancers. This study highlights curcuRouge®, an amorphous curcumin formulation, as a promising approach with superior bioavailability compared to other advanced commercial curcumin products. Amorphization of curcumin's molecular structure enhances both stability and bioavailability, positioning curcuRouge® as a significant advancement in curcumin delivery systems. Its rapid absorption and improved pharmacokinetic profile suggest potential clinical benefits, although further efficacy studies are needed to confirm therapeutic advantages. Comparative analysis indicates curcuRouge® offers exceptional systemic bioavailability and safety at modest doses, making it a strong candidate for effective therapeutic applications. Future research will be essential to establish its full clinical potential and broaden its application in health and disease management.

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Authors' contributions: MPK— Conceptualization, investigation, formal analysis, writing-original draft, writing-review and editing, visualization; TH— conceptualization, investigation, writing-review and editing, funding acquisition; YK— investigation, writing-review and editing, project administration, supervision; HA— formal analysis, investigation, writing-review and editing; KT – investigation, writing-review and editing; AK—investigation, writing-review and editing, project administration; All authors have read and agreed to the published version of the manuscript.

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