

A comparative pharmacokinetic evaluation of bioavailable curcumin formulation Curene[®] with curcumin formulation containing turmeric volatile oil and standard curcuminoids 95% in healthy human subjects

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ABSTRACT

Background: Curcumin, a major active component of turmeric, is one of the most studied botanicals for its numerous health benefits and high safety profile. In spite of its potential clinical health benefits, its applications are limited due to its poor bioavailability. The current study was carried out to compare the oral bioavailability of the newly developed bioavailable curcumin formulation Curene[®] with a curcumin formulation containing turmeric volatile oil (CP-01) and standard curcuminoids 95% in healthy human volunteers.

Methods: In this current open-label, randomized, three-treatment, single oral dose, single-period, parallel, comparative pharmacokinetics study, 12 healthy male volunteers participated. The test product Curene[®] (test treatment - T), reference products CP-01 (reference treatment - R₁) and standard curcuminoids 95% (reference treatment - R₂) were orally administered as a single dose

of 3 grams per subject. Plasma samples were withdrawn from each subject at predetermined time points, and samples were analyzed by LC-MS/MS.

Results: Based on the pharmacokinetics data, Curene[®] (Free curcumin; AUC_{0-t}) was found to be ~112.7 times more relatively bioavailable when compared to the standard curcuminoids (R₂).

Conclusion: The oral bioavailability of Curene[®] was found to be significantly higher compared to CP-01 and standard curcuminoids (95%). Furthermore, Curene[®] was also found to be safe in healthy human subjects under the study conditions.

Keywords: Absorption, bioavailability, Curene[®], pharmacokinetic

BACKGROUND

Turmeric (*Curcuma longa Linnaeus*) is one of the most revered medicinal plants in Ayurveda, the Indian traditional medicinal system. Turmeric includes the three curcuminoids: curcumin (ca. 75%), demethoxycurcumin (ca. 15%), and bisdemethoxycurcumin (BDMC) (ca. 5%). Curcumin is the major active constituent of turmeric, accounting for 75% of total curcuminoids, and it is responsible for turmeric's vibrant yellow color [1, 2]. Curcumin is reported to possess potent biological and pharmacological effects including antioxidant, anti-inflammatory, antimicrobial, and anticarcinogenic activities. Additionally, the hepatic and nephroprotective, thrombosis suppression, myocardial infarction protective, hypoglycemic, and antirheumatic effects of curcumin are also well established [3]. Curcumin is considered multi-functional in its therapeutic activities and is also found to be pharmacologically safe [4]. Curcuminoids have been listed by the US Food and Drug Administration (USFDA) as "Generally Recognized as Safe" (GRAS), and good tolerability and safety profiles have been shown in clinical trials, even at doses up to 12,000 mg/day [5]. Currently, curcumin is one of the most widely studied phytochemicals with great clinical potential to be developed as a botanical drug for multiple diseases [6].

However, there is a hurdle on the way to enjoying all of turmeric and curcumin's incredible health benefits due to their poor absorption, rapid biotransformation, and systemic elimination, which have often been cited as a reason for limited bioavailability and thereby poor therapeutic efficacy. Effective methods are being implemented to achieve enhanced bioavailability. Several strategies have been tested to improve bioavailability of curcumin by various mechanisms, most of which have been developed to block the metabolic pathway of curcumin in order to increase its bioavailability [5]. The absorption can be intensified by formulating curcumin in different forms to overcome the challenge of poor absorption including through nanocrystals, emulsions, liposomes, self-assemblies, and nanogel encapsulation in a liposome, polymeric nanoparticles, cyclodextrin encapsulation, lipid complexes or by synthesis of the polymer-curcumin complex.

All of them have helped increase bioavailability and been shown to improve the beneficial effect of curcumin [7].

Numerous studies have shown that by encapsulating curcuminoids into a microemulsion or nanoemulsion system, both solubility and stability of curcuminoids can be greatly enhanced [6]. Formulations developed using food-grade ingredients to enhance the absorption of curcumin have been studied in human clinical trials [1].

In the last decade, numerous bioavailability and curcumin metabolism studies in both *in vitro* models and animals have been performed to enhance the therapeutic efficacy of curcumin [8]. Co-administration of curcumin with an extract obtained from black pepper has been shown to increase the absorption area under the curve (AUC) of curcumin in animal studies. In another animal study, a complex of curcumin and phospholipids increased absorption of curcumin 3.4-fold, and the formulations of curcumin with surfactants were shown to increase the absorption of curcumin in mice [9]. Nanoparticles of Poly(lactic-co-glycolic acid) (PLGA) and PLGA-polyethylene glycol (PLGA-PEG) blend were shown to increase curcumin absorption in rats [10]. The combination of curcuminoids and volatile oil of turmeric rhizome triggered a 6.9-fold increase in a human pharmacokinetics study. The inclusion of curcumin in a lipophilic substance has been shown to increase the relative intestinal absorption of curcumin in human subjects [11]. A number of other strategies, such as the inhibition of curcumin metabolism by adjuvants have been investigated for their potential to enhance the biological availability of curcumin [12].

In view of the overwhelming coverage on these topics in literature, the foremost objective of the present study was to evaluate the oral bioavailability of bioavailable curcumin formulation Curene[®], 3 g (500 mg x 6 capsules), in comparison to CP-01, 3 g (500 mg x 6 capsules), and standard curcuminoids 95% 3 g (500 mg x 6 capsules) in healthy adult human male participants under fasting conditions.

METHODS AND MATERIALS

Study subjects

A total of 12 healthy adult male human volunteers having a BMI of 21.89 ± 2.52 kg/m² and aged 18-45 years participated in this study. Written informed consent was obtained and the study was approved by the Naithika Independent Ethics Committee. All subjects were asked to maintain their regular lifestyles and usual extent of physical activities during the study period.

Study design

This design was an open-label, randomized, three-treatment, single oral dose, single-period, parallel, comparative bioavailability study of Curene[®], CP-01, and standard curcuminoids 95% in healthy adult human male study participants under fasting conditions.

Study material

Curene[®] (Batch No: CUR/08/CAP/01) was manufactured by Olene Life Sciences Pvt. Ltd., Chennai, India. CP-01 (Batch No: VM-B7/17-18), manufactured by Livlong Nutraceuticals Ltd, India, was procured from the market. Standard curcuminoids 95% was procured from Plant Lipids Ltd, India, and was encapsulated by Olene Life Sciences Pvt. Ltd., India. Curene[®], CP-01, and standard curcuminoid were referred as test treatment (T), reference treatment (R₁) and reference treatment (R₂) respectively in this study. Volunteers were orally administered with a single dose of 3 g (6 capsules of 500 mg each) of the test product and reference products.

Study procedure

Prior to testing, each volunteer underwent screening and a consent visit to ensure eligibility and voluntary willingness to participate in the study. Volunteers included in the study complied with inclusion and exclusion criteria (shown in Table 1) and were found to be healthy on physical examination along with laboratory investigation.

All participants fasted overnight for a minimum of 10 hrs, and the test and reference products were administered orally in a staggered manner. Study products were administered orally with 240 ± 2 ml of water at room temperature in a sitting posture under the supervision of a medical practitioner. The study personnel ensured that the study participants had swallowed the study products by performing mouth and hand check.

Water intake was not allowed 1 hr. before dosing until 01.00 hr. after dosing except while administering the dose. After dosing, the participants remained in sitting position for the first four hrs. Thereafter, standard turmeric-free meals were provided at 04.00, 08.00 and 13.00 hrs. post-dose (i.e. lunch, snacks, and dinner respectively) on day 1. Standardized turmeric-free meals were the same for all study participants.

Participants were allowed to engage in normal activities without any physical exertion throughout their stay in Clinical Pharmacology Unit (CPU) during the study period. The movements of the participants inside the CPU were supervised by the clinical staff and when required, participants were escorted to toilets to prevent any untoward incidents.

Vital signs (blood pressure (BP), pulse rate, respiratory rate and oral temperature) were measured in study participants and recorded at the time of admission into the CPU according to protocol during the duration of the study.

BP, oral temperature and pulse rate were examined within 90 minutes prior to administration of study products and also measured at 12.00 hrs. post-dose (±30 minutes). BP and pulse rate were checked at 02.00 and 06.00 hrs. post-dose. Vital parameters were measured within 90 minutes prior to checkout (i.e. at 24.00 hrs. post-dose).

The blood samples were collected from each study participant. The pre-dose samples (0.00 hrs) were collected within 01.00 hrs. prior to study products administration and the others at 00.50, 01.00, 01.50, 02.00, 03.00, 04.00, 06.00, 12.00, 18.00 and 24.00 hrs. post-dose.

Table 1. Inclusion and exclusion criteria. Those who met all the inclusion and none of exclusion criteria were verified by investigators as per source documents, and those volunteers were admitted into the study.

Inclusion Criteria
<ul style="list-style-type: none"> ● Subjects who provided written informed consent. ● Subjects who were healthy adults within 18-45 years of age (inclusive). ● Subjects who had a Body Mass Index (BMI) ≥ 18.5 and ≤ 24.9 kg/m² with body weight at least 55 kg for men. <ul style="list-style-type: none"> ● Subjects who had systolic blood pressures with upper limits of less than 140 mmHg and lower limits of more than or equal to 100 mmHg. Similarly, subjects who had diastolic blood pressure with upper limits less than 90 mmHg and lower limits more than or equal to 70 mmHg. <ul style="list-style-type: none"> ● Subjects who had heart rates not less than 60 beats/min and not more than 100 beats/min and respiratory rate not less than 14 breaths/min and not more than 18 breaths/min. ● Subjects who were willing to take turmeric-free food for the trial duration. ● Subjects who had normal health as determined by medical history and physical examination performed within 21 days prior to the dosing for the study. <ul style="list-style-type: none"> ● Subjects who had normal ECG, chest X-ray, and vital signs. ● Subjects who were available for the entire study period and willing to adhere to protocol requirements as evidenced by written informed consent.
Exclusion Criteria
<ul style="list-style-type: none"> ● Subjects who were incapable of understanding the informed consent. ● Subjects who had history of difficulty in swallowing capsules. ● Subjects who had a history of hypersensitivity or idiosyncratic reaction to study medication or any other related drug, or to milk. <ul style="list-style-type: none"> ● Subjects who had any evidence of impairment of renal, hepatic, cardiac, pulmonary, or gastrointestinal function. Study volunteers with a history of tuberculosis, epilepsy, asthma (during past 5 years), diabetes, psychosis, or glaucoma. <ul style="list-style-type: none"> ● Subjects who regularly smoke more than 10 cigarettes per day or had difficulty in abstaining from tobacco for the duration of study period. ● Subjects who had taken over-the-counter or prescribed medications, including any enzyme-modifying drugs (known to induce or inhibit hepatic enzyme activity) or any systemic medication within the past 30 days prior to dosing in the study. <ul style="list-style-type: none"> ● Subjects who had a history of any psychiatric illness, which may impair the ability to provide written informed consent. <ul style="list-style-type: none"> ● Subjects who had a history of alcohol or drug abuse within the last 5 years. ● Subjects who had clinically significant abnormal values of laboratory parameters. ● Subjects who participated in any other clinical investigation using experimental drug(s) or had bled more than 350 mL in the past 3 months. <ul style="list-style-type: none"> ● Subjects who were unable or unlikely to be compliant with protocol requirements or restrictions. ● Subjects in whom study medication was contraindicated for medical reasons. ● Subjects who are or have been intolerant to venipuncture.

Ethics committee

All subjects provided written informed consent prior to undergoing any test related to this study. The study protocol was approved by the Naithika Independent Ethics Committee in accordance with the provisions of the current version of the ICH Good Clinical Practice and the US Code of Federal Regulations Guidelines for Good Clinical Practice (21 CFR parts 50 and 56), the current principles enunciated in the Declaration of Helsinki, requirements of CDSCO, Schedule Y and its amendments, and ICMR Ethical Guidelines for Biomedical Research on Human Participants (2006).

Blood sampling and collection

Blood samples were collected by using intravenous cannula for up to 06.00 hrs. post-dose and the remaining blood samples were collected by means of direct, sterile venipuncture using pre-labeled 4 ml K₂EDTA Vacutainers[®]. Blood samples were collected within 2+ minutes of specified sampling time. The actual clock time of each blood drawn was recorded on the Case Report Forms (CRF).

To ensure the patency of intravenous cannula, 0.5 ml of normal saline was injected into the cannula after each sample withdrawal, and this procedure was followed until blood up to 04.00 hrs. post-dose was drawn. Each blood sample was collected after discarding the first 0.5 ml saline-mixed blood. Blood samples were withdrawn by direct sterile venipuncture in case of cannula blockage or in case there was any reason blood could not be withdrawn through the cannula. All Vacutainers[®] used to collect blood samples for analysis were pre-labeled with the study number, tube number, study participant identification, period and sampling time point for the collection.

Sample preparation

After collection, the blood samples were placed in Thermocol box containing ice packs. Blood samples were centrifuged at 3,800 rpm for 10 minutes at 2°C to 8°C for separating the plasma. Centrifugation of all samples was done within 30 minutes of their withdrawal. All plasma samples were separated and divided into two aliquots in properly labeled polypropylene tubes and immediately stored at -20°C to 4°C until completion of analysis. The time from sample collection to placement in the freezer did not exceed 120 minutes.

Extraction procedure of curcumin

Plasma samples were extracted with ethyl acetate for curcumin, and the solvent used for the extraction was evaporated under the stream of nitrogen. The residue was reconstituted with 0.2 ml of mobile phase and then vortexed. The sample was transferred into auto-injector vials, and the vials were loaded into an auto-sampler. Then, 20 µl was injected into the LC-MS/MS.

Curcumin analysis

The blood plasma samples were analyzed for free curcumin by a validated LC-MS/MS method.

Statistical analysis

The pharmacokinetic parameters were calculated for curcumin using Phoenix[®] WinNonlin[®] version 6.4. The primary pharmacokinetic parameters included C_{max} , AUC_{0-t} , $AUC_{0-\infty}$ and secondary pharmacokinetic (PK) parameters included T_{max} and $t_{1/2}$. Statistical analysis was performed on pharmacokinetic data using SAS[®] Enterprise Guide hot fix 7.1, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA). The descriptive statistics (number, mean, standard deviation, minimum, maximum, median, % confidence value) were calculated for all the PK parameters for each test and reference treatments. Additionally, the geometric mean was calculated for primary parameters (C_{max} and AUC_{0-t}).

A linear mixed-effects model that includes fixed-effects terms for treatment and a random-effects term for subjects was used. In-transformed C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ of curcumin were calculated within the framework of this model; findings were consistent with the two one-sided tests for bioavailability, 90% confidence intervals for the difference between means test and reference treatments, and least-squares means for the comparison of test treatment (T) vs reference treatments (R_1) and (R_2). The differences and the confidence intervals were exponentiated to obtain point estimates of the test's ratio over reference geometric means and the 90% CI for the ratio, respectively. Test treatment T was compared to reference treatments R_1 and R_2 .

RESULTS

A total of 13 volunteers who were willing to participate in the study were enrolled. All the enrolled volunteers were selected. Out of 13 selected volunteers, 12 volunteers were admitted and 1 volunteer was not willing to participate. All admitted volunteers continued dosing in the study period. Study participants were randomized to the 3 treatments in a random order according to a randomization schedule. Study participant numbers were assigned from 1 to 12 in the order of the admission to the CPU. The flow diagram of the study is shown in Figure 1. The mean age (yrs), body weight (kg), height (cm), body mass index (BMI) (kg/m^2) for participated volunteers are presented in Table 2.

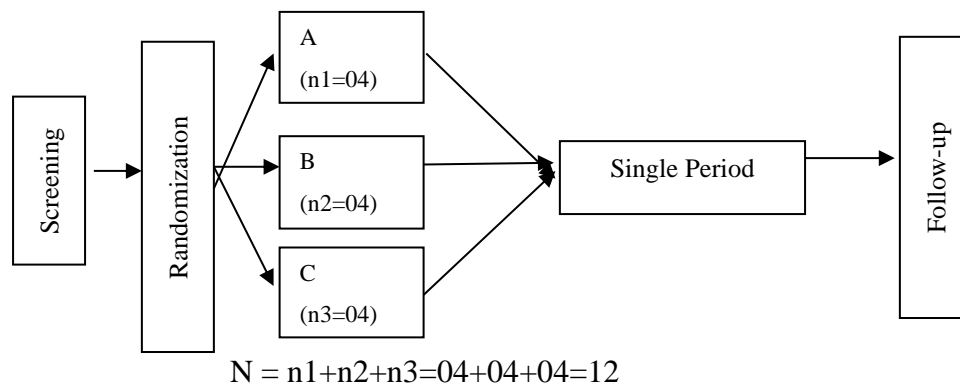


Figure 1. Flow diagram of the study.

Table 2. Demographics and other baseline characteristics.

	Age (yrs)	Weight (kg)	Height (cms)	BMI (kg/m ²)
Mean (SD)	32.08 (6.37)	59.37 (5.86)	164.87 (3.77)	21.89 (2.52)
Median	33.00	58.55	164.00	22.05
CV%	19.87	9.88	2.29	11.49
Range	21.0 - 40.0	52.3 - 69	160 - 174	18.6 - 24.9

The current study was carried out to evaluate the oral bioavailability of Curene[®] in comparison with CP-01 and standard curcuminoids 95% in healthy human adult male volunteers. For each formulation, the pharmacokinetic data of the free curcumin was plotted on a plasma concentration vs time curve and is presented in Figure 2. The area under the plasma concentration time curve (AUC), C_{max}, t_{max} and relative bioavailability (F) were calculated for all three formulations. Mean C_{max} values (standard deviation) of curcumin for Curene[®], CP-01 and standard curcuminoids 95% were found to be 1,545.83 (672.92), 190.29 (111.22) and 86.41 (29.57) pg/ml respectively. The mean C_{max} of Curene[®] was significantly (p<0.05) higher than the reference products. The T_{max} was found to be 2.50 hrs. for Curene[®], 2.25 hrs. for CP-01, and 2.25 hrs. for standard curcuminoids 95%. Mean curcumin AUC_{0-t} (standard deviation) was 6,302.85 (3,451.58) for Curene[®], 445.05 (318.79) for CP-01 and 206.62 (215.38) pg.h/ml for standard curcuminoids 95%. The log-transformed AUC_{0-t} for Curene[®] was observed to be statistically significant (p<0.05) when compared with reference products. Curene[®] was found to be ~12.7 times more bioavailable when compared to the R₂.

All three products were found to be equally well tolerated when administered orally under fasting conditions in healthy adult human subjects.

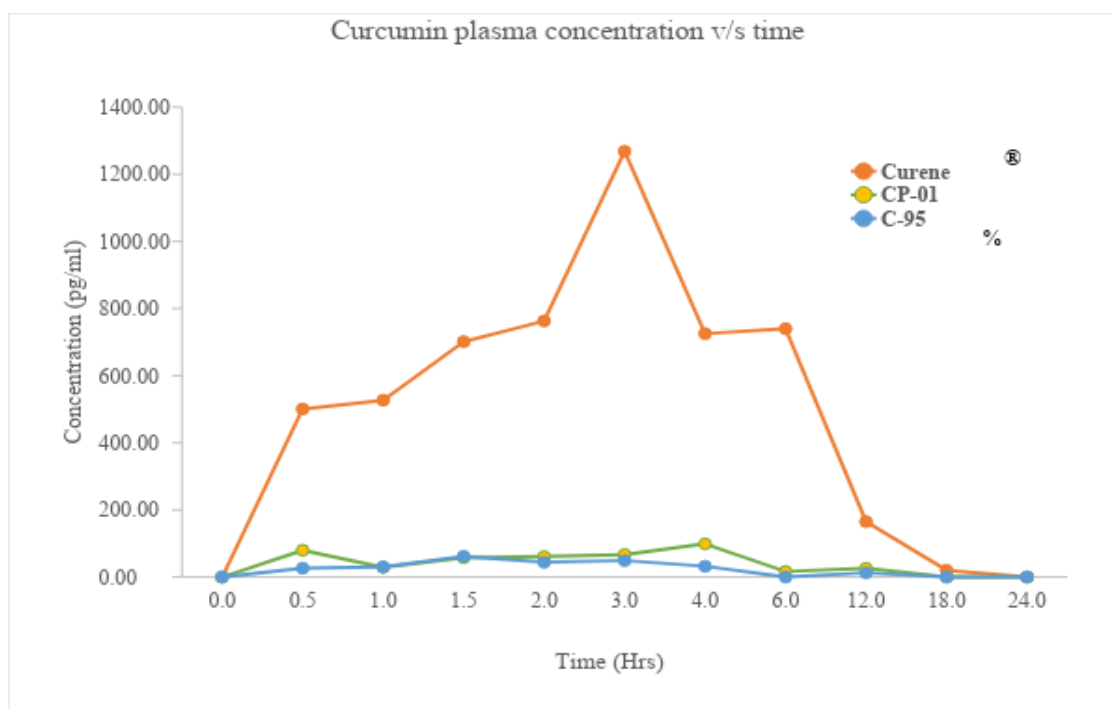


Figure 2: Mean plasma curcumin concentrations versus time plot – linear scale.

DISCUSSION

Curcumin is one of the most studied phytochemicals due to its high safety profile and multiple biological activities. It is one of the major active ingredients of turmeric accounting up to 75% of total curcuminoids present in turmeric.

Despite of its well-documented therapeutic efficacy, the limited oral bioavailability has hindered its development as a potential therapeutic agent. Efforts have therefore been dedicated toward developing curcumin formulations with enhanced oral bioavailability such as curcumin nanoparticles, nanogel formulations, liposomal formulations, and curcumin micelles with significant success [13]. A formulation of curcumin with a combination of hydrophilic carriers, cellulosic derivatives, and natural antioxidants has also been shown to significantly increase oral bioavailability [1]. Another approach to increase curcumin absorption involved combining curcuminoids and essential oils of turmeric rhizome to increase the absorption of curcumin with limited success [11]. Concomitant administration of piperine at the dose of 20 mg/kg increased the serum concentration of curcumin for a short period of 1-2 hrs. [14]. Recently, a novel formulation of curcumin using galactomannan fiber derived from the spice fenugreek was reported to augment the relative absorption of curcumin and was found to be 20 times higher in animals and 15.8 times higher in humans when supplemented orally [15].

Curcumin is known to have poor bioavailability even at higher doses. One of the strategies adopted to increase the bioavailability of curcuminoids is emulsification. Curene[®] is one such formulation that forms an emulsion similar to liposomes upon contact with the aqueous environment such as intestinal fluids. This emulsion is responsible for the higher solubility, absorption, and bioavailability of curcuminoids in Curene[®]. The reference compound R₁ is a blend of curcuminoids and turmeric essential oil. Essential oils do not enhance the absorption of curcuminoids and will just block the efflux of absorbed curcuminoids if any back into the intestinal lumen. The reference compound R₂, standard curcuminoids, are known to have poor intestinal absorption and hence poor bioavailability. Since this formulation will not lead to enhanced absorption of the curcuminoids, which is a primary requirement, it will not be effective in enhancing the bioavailability.

Herein, an attempt has been made to present an overview of the bioavailability of curcumin and its formulation that will be helpful for researchers and reviewers to consider this promising natural product as the forefront of therapeutic agents for management of human diseases in the near future. The vision of improving the bioavailability and the subsequent enhancement of curcumin's bioactivity by using a novel unique technique could monumentally alter the landscape of the research field as this will open up new avenues for its therapeutic application in various chronic illnesses.

CONCLUSIONS

Curene[®] was found to have higher bioavailability for free curcumin compared to CP-01 and standard curcuminoids 95%. The results of the present study also demonstrated that the Curene[®] is a highly safe curcumin formulation.

List of Abbreviations: AUC, Area under the plasma concentration-time curve; BP, blood pressure; CPU, Clinical Pharmacology Unit; Hour, hrs.; K₂EDTA, Dipotassium ethylenediaminetetraacetic acid; LC-MS/MS, Liquid chromatography-mass spectrometry

Authors' Contributions: SKP contributed to the design of the project, data analysis and was primarily responsible for writing the manuscript. VAP, S, and NM were involved in developing the patented formulation and the active drug product. TS and SS monitored the research.

Competing Interests: The authors have declared that there are no conflicts of interest. This study was funded by Olene life Sciences, Chennai, India.

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