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Research Article

Bioavailability Study of Maxicuma Capsules Versus Micronized Curcumin Capsules as A Single Oral Dose in Fasted Healthy Adult Human Subjects

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Abstract

Aim: The purpose of this study is to evaluate and compare the amount of free Curcumin in the human blood plasma after administration of three Capsules of Maxicuma 500 mg and three Capsules of Micronized Curcumin 95% each 500 mg as single dose in fasted healthy adult human subjects. The results of the study are also compared with plasma concentration of free Curcumin by Standard Curcumin as reported in the literature.**Methodology:** Comparative bioavailability of free curcumin for three Capsules of Maxicuma 500 mg and three Capsules of Micronized Curcumin 95%, (500) mg was evaluated in an open label, non-randomized, two-treatment, two-period, two-group crossover study after single oral dose administration in 14 fasted healthy adult humans. The free Curcumin was determined along with pharmacokinetic parameters such as Cmax, AUC0-t, T1/2, , Tmax. Linear & Semi log graphs were plotted with the help of SASR®. **Results:** Data from the study reveals that the maximum measured plasma concentration of free Curcumin was 195.196 ng/mL for Maxicuma and 81.270 ng/mL for Micronized Curcumin 95%. The times where maximum plasma concentration of free Curcumin achieved for the Maxicuma and Micronized Curcumin 95%, were 3.129 hours and 4.750 hours respectively. **Conclusion:** Maxicuma composition was 3.11 fold more bioavailable, in terms of free Curcumin level, as compared to Micronized Curcumin 95% and based on the literature study, provides 172 times more bioactive free Curcumin when compared to Standard Curcumin 95%.

Trial registration: CTRI/2021/12/038530 [Registered on: 09/12/2021]

Keywords: Free curcumin; Bioavailability; Maxicuma; 95% Curcuminoids; Human Subjects; Standard curcumin Extract powder 95%.

Introduction

Curcumin, yellow colored pigment present in turmeric, is proven to be beneficial in wide range of therapeutic areas. Curcumin is found to be effective in many health benefits including anti-inflammatory [1,2] and antioxidant effects, cancer protective properties (chemoprevention) [3,4,5] anti-bacterial, anti-viral and anti-fungal properties [1,6], liver [4] and kidney protection [7], cognitive properties [8], and having antidepressant [9], antidiabetic [10] and immune modulating properties [11]. While it has demonstrated potent health benefits in in-Vitro tests, one needs to administer much larger dose, such as 2-8gms/day to achieve any measurable health benefits upon oral administration. Main reason for the requirement of such large dose is its poor bioavailability, instability in gastrointestinal tract and quick, extensive metabolism in the intestine as well as liver to form inactive metabolites. There are number of research papers which suggest that the free or unmetabolized form of Curcumin is much more effective than the conjugated glucuronide or sulphate metabolite. The free form of Curcumin is found to be biologically active molecule, whereas in the conjugated forms or metabolites have little or no biological activity [12, 13].

Maxicuma is a 40% Curcumin composition made with natural excipients. In the current study, free Curcumin content is measured along with Curcumin metabolites in the plasma with and without use of glucuronidase/sulphatase enzymes. The plasma concentrations of Maxicuma composition is compared with reference Micronized Curcumin, which is micronized by passing through 80 mesh. Previously, Maxicuma has been subjected to pharmacokinetic evaluation in Wistar rats in comparison with Standard Curcumin 95%. This (unpublished) study revealed Tmax for Maxicuma was 1h with a highest concentration of 17.85 ng/mL and AUC of 623.8 ng.hr/L; similarly the 95 % Curcuminoids estimation revealed that the Tmax was at 1h with Cmax of 4.18 and lesser AUC of 208.8 ng.hr/L. The % relative bioavailability of free Curcumin of Maxicuma was 298.75 % which that of reference micronized curcumin 95%. In addition, Maxicuma was also evaluated for the single dose oral toxicity study in rats and mice after oral administration. There was no abnormality and gross lesions were present in any of the mice and rats with highest dose of 2000 mg/kg. NOAEL of Maxicuma was also deciphered at 440 mg/kg and 220 mg/kgb.wt. in rats and rabbits repeated dose 28 days toxicity study respectively.

Currently there are a just few compositions of Curcumin which do not use the glucuronidase/sulphatase in their bioanalytical methodology and show significant levels of free Curcumin in the plasma [14-16].

Methods

Subjects

The present clinical study was conducted in healthy, adult, human subjects of age 18 to 45 years (Male: 34.43 ± 5.83 Years; Female 29.57 ± 6.24 years) recruited from the pool of healthy volunteers. A total of 14 healthy subjects were enrolled. Subjects from the pool of healthy volunteers who were screened within 21 days prior to the first dosing day has been considered as potential participants in the study. Volunteers were only admitted to the study after having signed the informed consent form. There was no subject drop out observed during the study duration. The protocol was approved by ANVESHHAN Independent Ethics Committee, B-8, Simandhar Residency, Near Gulab Tower, Behind Utopia School, Thaltej, Ahmedabad-380054. Gujarat, India. The study protocol was approved bearing IEC no. ARL/CSP/2021/001-00 [IEC approved on: 29/11/2021]. Subjects were acquired at clinical site Macleods Pharmaceuticals Ltd., Bioequivalence Department, R&D IV, 5th Floor, Empire Doctor House, Opp. Kargil Petrol Pump, Science city road, Sola, Ahmedabad 380 060, India.

Inclusion Criteria

1. Healthy volunteers within the age range of 18 to 45 years (both inclusive).

2. Presently non-tobacco users (smokers and chewers).

3. Willingness to provide written informed consent to participate in the study.

4. Body-mass index (BMI) between 18.50 kg/m^2 and 29.99 kg/m^2 (both inclusive) with body weight not less than 50 kg (for males) and with body weight not less than 45 kg (for females).

5. Absence of significant disease or clinically significant laboratory values or laboratory evaluation, medical history or physical examination during the screening.

6. Have a normal 12-lead ECG or one with abnormality considered to be clinically insignificant.

7. Have a normal chest X-ray PA view or one with abnormality considered to be clinically insignificant.

8. Willing to take turmeric free food for the entire study duration.

9. Comprehension of the nature and purpose of the study and compliance with the requirement of the distributed ICF.

10. Volunteer is regularly menstruating / Volunteer is in postmenopausal phase for at least 1 year / is surgically sterile (for females).

11. Volunteer of child bearing potential practicing an acceptable method of birth control for the duration of the study as judged by the investigator(s) such as condoms, foams, jellies, diaphragm, and intrauterine device (IUD) or abstinence etc. except hormonal contraceptives (for females).

Exclusion Criteria

1. Personal history of allergy or hypersensitivity to Curcumin or to any components of the formulation or allied drugs or excipients.

2. Any major illness in the past 90 days or any clinically significant ongoing chronic medical illness e.g. Congestive Cardiac Failure, Hepatitis, Hypotensive episodes, Hyperglycemia etc.

3. Presence of any clinically significant abnormal laboratory values during screening e.g. significant abnormality of liver function test, renal function test etc.

4. Severe cardiac, renal or liver impairment, gastro-intestinal disease or other conditions, any other organ or system impairment.

5. History of seizures, epilepsy or any kind of Neurological disorders.

6. History of hypercalcemia or vitamin D toxicity.

7. Past history of Anaphylaxis or angioedema.

8. Presence of disease markers of HIV or Hepatitis B or Hepatitis C virus.

9. History of chronic consumption of any kind of alcoholic beverages for more than 2 years or having consumed alcohol within 48 hours prior to check-in.

10. Consumption of products containing xanthine derivatives (chocolates, tea, coffee or cola drinks) or tobacco products within 48 hours prior to check-in.

11. Consumption of grapefruit or grapefruit containing products or any cruciferous vegetables (e.g. broccoli, brussels sprouts, etc.) or char-broiled meat prior 7 days of investigational product administration.

12. Use of any recreational drug or a history of drug addiction.

13. Participation in any clinical trial within the past 90 days.

14. History of difficulty with donating blood or difficulty in accessibility of veins in left or right arm.

15. Donation of blood (one unit or 350 mL) within 90 days prior to receiving the first dose of study medication.

16. Consumption of any other prescription drug or over the counter (OTC) drugs (including vitamins and medicinal products from natural origin) within two weeks prior to receiving the first dose of study medication or repeated use of drugs within the last four weeks and throughout subject's participation in the study.

17. An unusual diet for whatever reason e.g. low sodium diet, for two weeks prior to receiving any medication and throughout subject's participation in the study.

18. Recent history of dehydration from diarrhoea, vomiting or any other reason within a period of 48 hours prior to the study.

19. Use of oral contraceptive in last 90 days (for females).

20. Pregnant / lactating volunteers (for females).

Study Material

Maxicuma 500 mg Capsules (Test) and Micronized Curcumin 95%, 500 mg Capsules (Reference) were obtained from India Glycols Ltd, NOIDA, India. This study includes analytical method validation not only for total Curcuminoids but also for metabolites such as glucuronides/sulphates (details are not included). Since Standard Curcumin 95% do not produce detectable free Curcumin plasma concentrations even at larger doses, it was decided to use Micronized Curcumin 95%, which, as per published research, has 9 -10 times higher bioavailability and can be easily quantified in plasma with minimum error [17].

Study Design

An open label, non-randomized, two-treatment, two-period, single dose, two-group crossover study on healthy, adult, human subjects under fasting condition. Duration of the study is 21 days including 14 days washout period. It is an open labelled study because there was no possibility to blind the appearance of the products. The analysts concerned, however, were informed regarding sequence of administration of test and reference product to the individual subjects. The order of receiving treatment was non-randomized, i.e., in period I, 3 male & 4 female subjects has been administered Maxicuma while 3 female & 4 male subjects has been administered Micronized Curcumin. In period II, crossover has been done. Subjects served as their own control, the study being of crossover design. The blood sampling time scheduled is intended to cover the expected Tmax of Total Curcuminoids of 1.00 hour as shown in the previous study. The last sample was collected at 24.00 hours post-dose, is more than 3 times the reported half-life of Total Curcuminoids (approximately 4.00 to 6.00 hrs), as per previous study data and covers at least 80% of the extrapolated AUC [18].

Study Procedure

An oral dose of three capsules of Maxicuma or Micronized Curcumin 95%, 500 mg were administered at 0.00 hour during each period. Maxicuma or Micronized Curcumin 95%, 500 mg administered with 240 mL (about 8 oz) of drinking water at room temperature under the supervision of the medical officer where

start time of the dosing was recorded in investigational product administration forms. The dosing interval between two consecutive subjects was 3 minutes.

Dosing has been done as per below;

In period I, 3 male & 4 female subjects had been administered three capsules (3 X 500 mg) of Maxicuma 500 mg Capsule and 4 male & 3 female subjects had been administered three capsules (3 X 500 mg) of Micronized Curcumin 95%, 500 mg Capsule.

In period II, crossover was done after 14 days wash out period. 4 male & 3 female subjects had been administered three capsules (3 X 500 mg) of Maxicuma 500 mg Capsule and 3 male & 4 female subjects had been administered three capsules (3 X 500 mg) of Micronized Curcumin 95% 500 mg Capsule.

Bioanalytical Method

Samples were analysed using validated LC-MS-MS analytical method. During analysis all three curcuminoids, viz. Curcumin, Demethoxycurcumin and Bisdemthoxycurcumin were measured along with their metaboliotes, including Tetrahydrocurcumin, Glucuronides and Sulphates, with and without glucuronidase/ sulphatase enzymes. The results of analysis are presented to cover Free Curcumin as well as Free Curcuminoids.

Meal Plan

After check-in, subjects has received standardized meal was provided approximately at -36.00 (i.e. dinner) on Day -2, -24.00, -20.00, -16.00 and -12.00 hours (i.e. breakfast, lunch, snacks and dinner) on Day -1. A standard meal (comprising of 2600 - 3000 Kcal) was provided approximately at 4.00, 8.00 and 12.00 hours post-dose on dosing day (day 1) (i.e. lunch, snacks and dinner), standard meal (2600-3000 Kcal) was provided approximately at 24.00, 28.00 and 32.00 hours post dose on day 2 (i.e. breakfast, lunch and snacks) during each period.

Blood Sampling Schedule:

Blood samples (each of 5 mL) were collected in 5 mL blood collection tube containing K3EDTA as anticoagulant during each period. The venous blood samples had been withdrawn at -06.00 hours, pre-dose and at 00.25, 00.50, 00.75, 01.00, 01.33, 01.67, 02.00, 02.50, 03.00, 03.50, 04.00, 06.00, 08.00, 12.00, 16.00 and 24.00 hours post-dose.

Statistical Analysis

Summary statistics, ANOVA, Intra-subject variability, 90% Confidence interval and Power was calculated using SAS® Linear software. Descriptive statistics has been provided for all pharmacokinetic parameters for Total Curcuminoids tests and reference compositions. Since this is a proof-of -concept design, the outcomes are not evaluated for statistical significance.

Results

Primary pharmacokinetic parameters of free curcuminoids were evaluated for all the samples. For Curcumin, mean of AUCt Micronized Curcumin 95% was 863.27 (ng.h/ml) whereas for MAXICUMA 2686.16 (ng.h/ml) was observed. % Relative bioavailability of curcumin in case of Maxicuma was found to be 311.16%.

For BDMC, mean of AUCt Micronized Curcumin 95% for was 29.33 (ng.h/ml) whereas for MAXICUMA 83.78 (ng.h/ml) was observed. % Relative bioavailability of BDMC in case of Maxicuma was found to be 285.61%.

For DMC, mean of AUCt for Micronized Curcumin 95% was 270.93 (ng.h/ml) whereas for MAXICUMA 846.91 (ng.h/ml) was observed. % Relative bioavailability of DMC in case of Maxicuma was found to be 312.58%.

For THC, mean of AUCt for Micronized Curcumin 95% was 367.41 (ng.h/ml) whereas for MAXICUMA 1707.57 (ng.h/ml) was observed. % Relative bioavailability of THC in case of Maxicuma was found to be 464.76%.

Since Maxicuma is at 40% concentration as compared to Micronized Curcumin which is at 95% concentration, a correction factor of 2.375 has been applied to determine the exact fold increase in the bioavailability. With this correction, Maxicuma shows 678.32% increase in relative bioavailability as compared to Micronized Curcumin.

For COG, mean of AUCt for Micronized Curcumin 95% was 224.84 (ng.h/ml) whereas for MAXICUMA 699.56 (ng.h/ml) was observed.

For COS, mean of AUCt for Micronized Curcumin 95% was 802.40 (ng.h/ml) whereas for MAXICUMA 7668.75 (ng.h/ml) was observed.

Discussion

Curcumin, the single most active principle of Turmeric has gained popularity in recent times for its health benefits such as anti-inflammatory effect in bone health, neuroprotective effects, immunomodulatory effects, anticancer effects and many more. While Curcumin effects are exemplary in *in-Vitro* and cell-line studies at low concentrations, its health benefits in *in-Vivo* animal studies and human clinical trials cannot be demonstrated even at large doses. Main reasons for the lack of efficacy in *in-Vivo* or human trials are a) instability of Curcumin in various physiological pHs in the intestine leading to its significant destruction in the

gastrointestinal tract, b) poor absorption due to insolubility of Curcumin in gastro-intestinal fluids and c) extensive metabolism of Curcumin in gastrointestinal tract as well as in the liver to inactive metabolites. Due to these reasons, about 50% of curcuminoids are excreted in feces unabsorbed, less than 1% of the absorbed Curcuminoids can be found in the blood plasma in unmetabolized form even with large doses [19] and 10-15% of the Curcuminoids are degraded in the gastrointestinal tract before being absorbed. Unless all three above mentioned issues are addressed, one cannot realize high therapeutic potential of Curcumin in a clinical trial.

Numerous attempts have been reported in the literature that address one or more of the above listed issues [20]. Micronization, microencapsulation with hydrophilic films, use of high amounts of surfactants, molecular dispersion, micellization, complexation, entrapment in fibers, entrapment in micro tube structures, solid-lipid nanoparticles, liposomal technology, use of piperine to limit metabolism etc. have been tried to enhance the efficacy of Curcumin, but with limited success. Reason being, none of these technologies address all the three issues listed above. Most Curcumin compositions developed in recent times address poor absorption and very few on protecting Curcumin from harsh physiological conditions and microsomal enzymes. Net result being low concentration of unmetabolized or free curcumin in plasma/serum even with large doses. Only Longvida, with 80% phospholipid composition and CurQfen, a complex with fenugreek soluble fibers, have been able to show reasonably higher concentration of unmetabolized or free Curcumin in plasma/serum during human bioavailability studies [15,16]. However, to achieve best therapeutic benefits in chronic inflammation, unmetabolized or free Curcumin should be even higher in concentration and should remain in plasma/serum for longer time, in other words, with a prolonged half-life. Longer plasma half-life will not only help in ameliorating chronic inflammation but also in developing One-A-Day tablet/capsule regimen, which is most desirable and consumer compliant.

Maxicuma, a unique Curcumin composition made with LIMAN (Lipid Matrix Nano encapsulation) technology [21], addresses all the issues of poor Curcumin efficacy. It provides high stability to curcumin at all the physiological pHs, prevents rapid metabolism of Curcumin, in gastrointestinal tract. Its plasma half-life is significantly longer than most Curcumin compositions reported in the literature.

In his study, we have chosen Micronized Curcumin rather than Standard Curcumin for comparison of bioavailability due to the fact that the later produces undetectable amounts of un-metabolized Curcumin in the plasma even with large dose. The Cmax value 0.074ng/ml and AUC 0.072ng-h/ml for Standard Curcumin are considered for comparison purpose from a past published study [22]. It has been established that Micronized Curcumin delivers 9-10 fold higher plasma concentration of Curcumin as compared to Standard Curcumin [17]. In this study, the plasma concentrations of Curcumin, Demethoxycurcumin, Bisdemethoxycurcumin and their metabolites are measured by LCMS/MS method without glucuronidase/sulfatase enzyme treatments. Tables 1 to 12 show the plasma concentrations of Curcumin, Demthoxycurcumin, Bisdemethoxycurcumn, Tetrahydrocurcumin, Curcumin glucuronides and Curcumin sulfates for Micronized Curcumin and Maxicuma.

Table 1 Pharmacokinetic Analysis – Free Curcuminoids: Curcumin-Micronized Curcumin 95%

Pharmacokinetic Parameters	Mean	Median	S.D.	C.V.	(Minimum - Maximum)
Cmax (ng/mL)	81.27	88.10	46.55	57.28	19.25 - 161.12
AUCt (ng.h/mL)	863.27	853.31	764.46	88.55	17.24 - 2112.03
AUCinf (ng.h/mL)	3384.69	2658.34	2443.66	72.20	410.12 - 6863.62
Tmax (h)	4.75	4.50	3.68	77.52	0.75 - 12.00
Thalf (h)	29.89	32.06	22.99	76.91	2.94 - 68.65

Table 2 Pharmacokinetic Analysis – Free Curcuminoids: curcumin-Maxicuma

Pharmacokinetic Parameters	Mean	Median	S.D.	C.V.	(Minimum - Maximum)
Cmax (ng/mL)	195.20	195.82	123.64	63.34	36.22 - 384.13
AUCt (ng.h/mL)	2686.16	2594.81	2199.67	81.89	147.67 - 5290.47
AUCinf (ng.h/mL)	8316.50	1751.65	10258.98	123.36	154.50 - 31252.36
Tmax (h)	3.13	2.00	2.63	83.94	0.25 - 8.00

Pharmacokinetic Parameters	Mean	Median	S.D.	C.V.	(Minimum - Maximum)
Thalf (h)	24.02	15.94	26.63	110.89	1.69 - 86.90

Table 3 Pharmacokinetic Analysis – Free Curcuminoids: BDMC- Micronised curcumin 95%

Pharmacokinetic Parameters	Mean	Median	S.D.	C.V.	(Minimum - Maximum)
Cmax (ng/mL)	2.56	3.02	1.21	47.46	0.74 - 3.98
AUCt (ng.h/mL)	29.33	32.87	20.43	69.67	1.00 - 54.89
AUCinf (ng.h/mL)	91.84	74.18	78.50	85.48	6.19 - 274.80
Tmax (h)	6.15	5.00	6.16	100.16	0.75 - 24.00
Thalf (h)	22.57	14.16	20.52	90.92	7.18 - 70.88

Table 4 Pharmacokinetic Analysis – Free Curcuminoids: BDMC- Maxicuma

Pharmacokinetic Parameters	Mean	Median	S.D.	C.V.	(Minimum - Maximum)
Cmax (ng/mL)	7.48	5.24	5.39	72.06	2.31 - 19.86
AUCt (ng.h/mL)	83.78	85.41	50.34	60.08	26.91 - 203.99
AUCinf (ng.h/mL)	182.50	184.78	103.82	56.89	32.72 - 357.51
Tmax (h)	6.60	6.00	4.88	73.97	1.33 - 16.00
Thalf (h)	32.43	21.23	32.92	101.51	4.78 - 113.37

Table 5 Pharmacokinetic Analysis – Free Curcuminoids: DMC- Micronised curcumin 95%

Pharmacokinetic Parameters	Mean	Median	S.D.	C.V.	(Minimum - Maximum)
Cmax (ng/mL)	32.56	33.88	20.26	62.21	2.65 - 64.91
AUCt (ng.h/mL)	270.93	277.18	228.20	84.23	4.06 - 619.48
AUCinf (ng.h/mL)	1177.76	796.29	1169.23	99.28	375.04 - 3532.79
Tmax (h)	6.95	6.00	6.70	96.42	0.75 - 24.00
Thalf (h)	32.25	18.20	35.56	110.27	8.55 - 103.32

Table 6 Pharmacokinetic Analysis - Free Curcuminoids: DMC- Maxicuma

Pharmacokinetic Parameters	Mean	Median	S.D.	C.V.	(Minimum - Maximum)
Cmax (ng/mL)	103.93	91.71	73.22	70.45	14.81 - 233.17
AUCt (ng.h/mL)	846.91	688.61	654.39	77.27	55.31 - 1797.19
AUCinf (ng.h/mL)	1420.59	1497.72	1036.06	72.93	179.56 - 3297.77
Tmax (h)	3.61	2.29	2.63	72.76	0.75 - 8.00
Thalf (h)	10.78	10.97	7.27	67.45	1.59 - 30.19

Table 7 Pharmacokinetic Analysis - Metabolites: THC- Micronised curcumin 95%

Pharmacokinetic Parameters	Mean	Median	S.D.	C.V.	(Minimum - Maximum)
Cmax (ng/mL)	35.26	23.38	36.90	104.67	4.33 - 115.50
AUCt (ng.h/mL)	367.41	321.95	323.18	87.96	12.10 - 1096.91
AUCinf (ng.h/mL)	761.37	720.49	649.40	85.29	133.37 - 1430.24

Pharmacokinetic Parameters	Mean	Median	S.D.	C.V.	(Minimum - Maximum)
Tmax (h)	15.71	16.00	2.92	18.58	12.00 - 24.00
Thalf (h)	16.16	8.72	18.72	115.85	2.30 - 37.45

Table 8 Pharmacokinetic Analysis - Metabolites: THC- Maxicuma

Pharmacokinetic Parameters	Mean	Median	S.D.	C.V.	(Minimum - Maximum)
Cmax (ng/mL)	133.93	141.03	91.93	68.64	25.89 - 302.62
AUCt (ng.h/mL)	1707.57	1585.46	1320.79	77.35	318.22 - 4794.17
AUCinf (ng.h/mL)	2213.33	1958.01	1856.03	83.86	596.21 - 5737.18
Tmax (h)	10.29	14.00	7.84	76.17	1.67 - 24.00
Thalf (h)	15.82	12.80	9.93	62.80	6.36 - 36.01

Table 9 Pharmacokinetic Analysis-Metabolites: COG- Micronised curcumin 95%

Pharmacokinetic Parameters	Mean	Median	S.D.	C.V.	(Minimum - Maximum)
Cmax (ng/mL)	31.10	32.30	5.17	16.62	13.65 - 35.48
AUCt (ng.h/mL)	224.84	236.10	53.75	23.91	126.44 - 287.58
AUCinf (ng.h/mL)	1612.95	1411.48	1509.40	93.58	240.70 - 6052.65
Tmax (h)	1.73	1.21	1.45	84.26	0.25 - 6.00
Thalf (h)	92.21	76.13	104.19	112.99	7.85 - 404.55

Table 10 Pharmacokinetic Analysis - Metabolites: COG- Maxicuma

Pharmacokinetic Parameters	Mean	Median	S.D.	C.V.	(Minimum - Maximum)
Cmax (ng/mL)	93.816	90.29	35.7851	38.14	37.17 - 175.24
AUCt (ng.h/mL)	699.55525	708.8299	121.074156	17.31	445.73 - 864.44
AUCinf (ng.h/mL)	3255.63593	3148.1601	1208.234571	37.11	1575.85 - 5394.11
Tmax (h)	1.546	1.33	0.7708	49.87	0.75 - 3.00
Thalf (h)	72.78818	68.0057	36.622078	50.31	19.80 - 135.43

Table 11 Pharmacokinetic Analysis - Metabolites: COS- Micronised curcumin 95%

Pharmacokinetic Parameters	Mean	Median	S.D.	C.V.	(Minimum - Maximum)
Cmax (ng/mL)	73.20	54.31	56.11	76.65	0.00 - 171.04
AUCt (ng.h/mL)	802.40	79.26	951.72	118.61	10.65 - 2423.62
AUCinf (ng.h/mL)	10694.82	1843.33	22348.09	208.96	63.63 - 56258.77
Tmax (h)	5.59	6.00	4.49	80.35	0.25 - 16.00
Thalf (h)	86.00	8.65	192.71	224.08	3.52 - 479.33

Table 12 Pharmacokinetic Analysis - Metabolites: COS- Maxicuma

Pharmacokinetic Parameters	Mean	Median	S.D.	C.V.	(Minimum - Maximum)
Cmax (ng/mL)	656.07	651.41	354.87	54.09	269.44 - 1323.63
AUCt (ng.h/mL)	7668.75	6278.80	7215.61	94.09	391.61 - 20203.03
AUCinf (ng.h/mL)	19746.06	16434.46	18589.93	94.14	716.33 - 48410.21
Tmax (h)	8.12	6.00	4.76	58.63	3.50 - 16.00
Thalf (h)	10.74	8.91	10.29	95.79	0.71 - 27.80

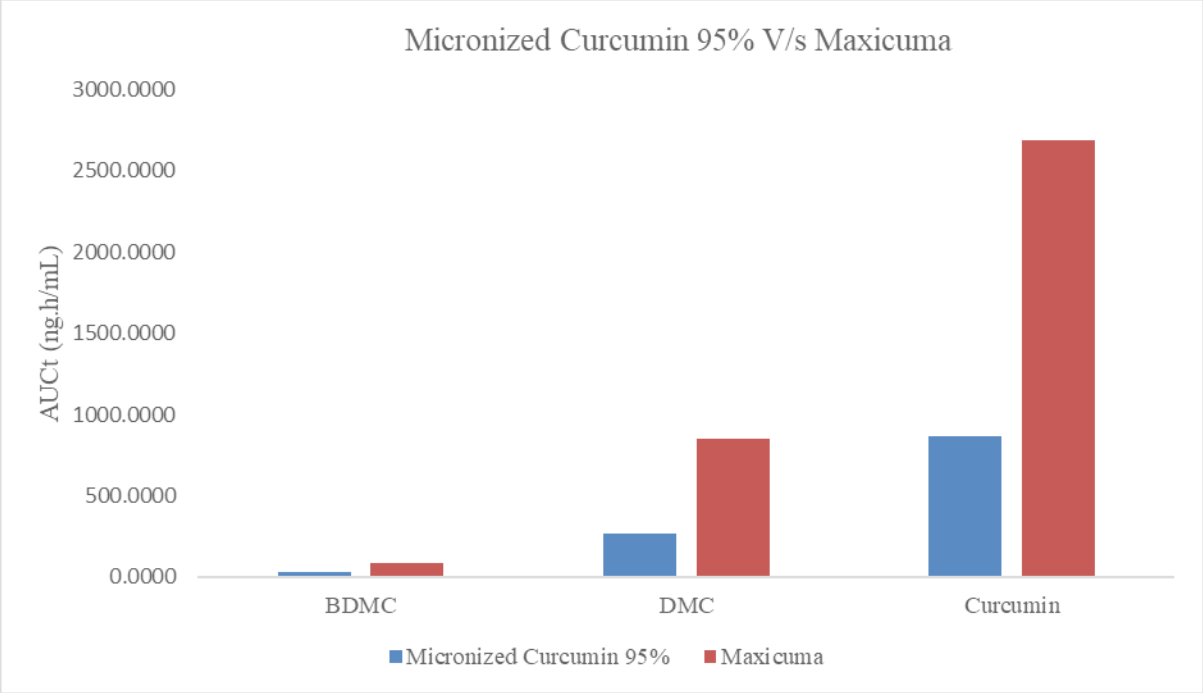
Table 13: Comparison of % Free or Unmetabolized Curcumin/ Total Curcumin, including metabolites.

Parameter	Maxicuma-40%	Curcumin 95%-Standard (Data taken from literature)
AUC data for Maxicuma –Free curcumin(ng.h/ml)	2686.16	0.072
AUC data for Total Curcumin (ng.h/ml) (Curcumin+ THC+ COG+COS)	12762.03	24.774
Ratio of free to total curcumin	21.04	0.29
Free Curcumin Fold	72.55	
With the Dose correction for Maxicuma (40%) and Curcumin (95%) , 95/40 =2.375	72.55 x 2.375 172.3 Fold	

This study emphasizes the importance of unmetabolized Curcumin (Free form of Curcumin) in plasma. There is ample evidence in the literature that reiterates the importance of unmetabolized Curcumin as most potent therapeutic agent as compared to its metabolites [12, 13]. Moreover, the metabolites such as glucuronides and sulphates are water soluble and are readily eliminated from the plasma within short duration [22,23]. Hence, for any therapeutic benefit, it is imperative consider the Free Curcumin concentration in plasma [24]. While Tetrahydrocurcumin, one of the major metabolites of Curcumin, is reported to have potent anti-inflammatory properties, has little contribution to the health benefits of Curcumin due to the fact that it too undergoes further metabolism to form glucuronides and sulphates and get eliminated from the plasma in a short duration [25]. Bisdemethoxycurcumin appears to be more stable, more potent and less metabolized, but it is occurs in low (3-5%) concentration among other curcuminoids [26].

In Tables 1 to 12, the data represents measurement of curcuminoids and metabolites in their free form in plasma without glucuronidase/ sulphatase enzyme. Further, the values of Curcumin, THC, COG and COS were considered for total curcumin calculation in the plasma. Though as mentioned above the curcumin metabolites, curcumin glucuronide and curcumin sulphate are analysed, but were not considered for the calculation of free Curcumin level and bioavailability. Thus, the current study provides concentrations of free Curcuminoid levels, rather than the concentrations of Curcuminoids plus metabolites, emphasizing the fact that it is free or unmetabolized Curcumin that renders desired therapeutic benefits of Curcumin.

Fig 1: Comparative AUC data of Curcuminoids



Maxicuma, at 40% Curcuminoid content has about 172 times higher amounts of free or unmetabolized Curcumin as compared to Standard Curcumin 95% (taken from literature data). With such high concentrations of plasma Free Curcumin, Maxicuma surpasses many other Curcumin compositions, such as Longvida or CurQfen, in delivering therapeutically potent form of Curcumin. At 40% Curcuminoid content, Maxicuma stands out as a composition providing highest strength of curcuminoids along with high physiological stability, high water solubility and highest concentration of plasma free Curcumin, that too in a One-a-Day tablet/capsule regimen. Superior water solubility of Maxicuma also makes it suitable for applications such as Shots and Ready-to-Drink beverages.

Conclusion

Maxicuma, with 40% Curcuminoids, delivers significantly high plasma concentrations of unmetabolized or free Curcumin as compared to Micronized Curcumin 95%. When compared with Standard Curcumin 95% (as reported in the literature), Maxicuma provides 172 times more free or unmetabolized plasma concentrations with a half-life well beyond 24 hours, making it suitable for one-a-day dosage regimen. Being water soluble, Maxicuma can easily be incorporated in to shots and ready-to-drink beverages.

Ethics approval and consent to participate

The study was conducted in accordance to all pertinent requirements of international, national bio ethics guideline and ICH 'Guideline for Good Clinical Practice', and in accordance with New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act, 1940, AYUSH and CDSCO requirement and Declaration of Helsinki (2013).

The study has been submitted to the ANVESHHAN Independent Ethics Committee, Ahmedabad with protocol no. ARL/CSP/2021/001-00 approved on date of 29th November 2021. This trial was also registered with clinical trial registration of India (CTRI) with registration number CTRI/2021/12/038530 [Registered on: 09/12/2021].

Consent for Publication

As no personal data are included in the present manuscript, this section is not applicable.

Availability of data and materials

As per our SOP, all the studies related data are archived for 9 years from the data of archival of the study at research facility Accuprec Research Labs Pvt. Ltd. Ahmedabad, India.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MR and RG has prepared the whole manuscripts. HP has prepared the tables, figures and appendices of the manuscript. JK has done the data analysis. AP has done the whole bio analysis for the present study. All the authors read and approved the final manuscript.

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