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Research Article

A Pilot Cross-Over Study to Assess the Human Bio Availability of "Cureit" A Bio Available Curcumin in Complete Natural Matrix

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ABSTRACT

Curcumin is a safe, effective and potential compound, finds its application as an ingredient for foods and medicines. In order to be effective as a medicine, it has to be more bio available than usual forms. Even though the concentration by composition is increased, it cannot be absorbed to the body- but, some formulations can.

Curcumin is found to have potential benefits on treatment and prevention of several diseases. But, the low bioavailability makes a barrier for its use. Cureit, a novel bio available Curcumin formulation, have developed naturally, of which, bioavailability is compared with that of normal Curcumin. It is found to be >10 fold more bio available than the normal Curcumin.

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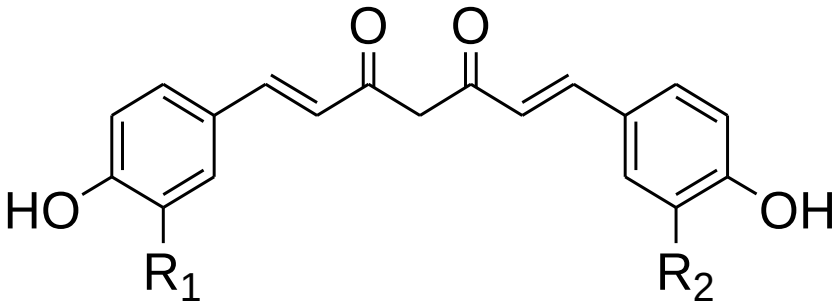
INTRODUCTION

Turmeric, the rhizome of herb *Curcuma longa* contains the natural polyphenols,called Curcuminoids, which includes Curcumin (diferuloylmethane; 1,7–bis[4-hydroxy-3-methoxyphenyl]–1,6-heptadiene-3,5-dione), demethoxy-Curcumin and bis-demethoxy- Curcumin. They are known to be responsible for the yellow color and the therapeutic activities of turmeric (Curcuma longa) [1]. The Curcuminoids are composed with approximately 77% Curcumin, 17% demethoxyCurcumin, and 6% bisdemethoxyCurcumin. It has been used as spice, colorant and as traditional medicine for many aliments such as cancer, Alzheimer's disease, inflammatory bowel syndrome, arthritis, etc[2,3,4]. Also, crcumin enhances the immune system. But Curcumin is limited in its clinical applicability by its low bioavailability during oral administration.



R_1 =R_2 = OMe, Curcumin (C1)
R_1 = OMe, R_2 = H, DemethoxyCurcumin (C2)
R_1 = R_2 = H, BisdemethoxyCurcumin (C3)

Fig.1

In Phase I clinical trials, dietary Curcumin was shown to exhibit poor oral bioavailability, due to insolubility in water, poor absorption, high rate of metabolism and systemic elimination.[5,6]. Many attempts have been made to enhance bioavailability of Curcumin by preparing it in novel formulations. Inhibition of metabolism and enhancement of water solubility together makes a potential effect.

Cureit is a unique potential formulation, which is devoid of liposomes, bio-enhancers, micelles, phospholipid complexes, structural analogues etc. Here, the bioavailability of Curcumin is increased by dietary fibres and water soluble proteins of turmeric, which enhances the bioavailability, as well as pharmacological effects. The current study focussed on the bioavailability of “cureit”. The study compares the bio availability of “cureit” in the blood plasma with respect to the control. The safety and tolerability of a single dose of cureit capsule is also monitored.

MATERIALS AND METHODS

“Cureit” capsules-500mg and the reference (control) are from Plant Lipids (P) Ltd. The solvents and chemicals are purchased from spectrochem.

Study design:
The Study Protocol and the corresponding informed consent of study subjects was reviewed and approved by the “Clinical Independent Ethics Committee” on 10-SEP-2013, before the first administration of study medication. The formal consent of a volunteer, using the ethics committee approved consent form, was obtained before the volunteer underwent any study specific procedure. This study was designed as a randomized, open label, balanced, single centre, two treatments, two periods, two sequence, single dose, crossover bioequivalence study.

12 human healthy male adults, of BMI within 18.50 to 30.00 Kg/m^2 in an age group of 18-45yrs old were included in the study. They were medically healthy, with clinically acceptable laboratory profiles, ECG and chest X-ray, and did not have any major disease during screening medical history and whose physical examination was performed within 21 days prior to the period one of testing. They were not participated in a bioavailability / bioequivalence / Pharmacokinetic study or received an investigational drug, especially containing Curcumin within a period of 3 months prior to study period. They were not habitual users of tobacco or alcohol, and were satisfying all the criteria for inclusion.

This study was a two period, two sequences, and two treatment study. A single oral dose of the test product and reference product were administered on 2 different days for the subjects. The first and second dosages were separated by a wash out period of 14 days. The duration of the study from the check-in of period-one to the last blood draw of period two was 15 days. Subjects were reported to the clinical facility from at least 11 hours prior to the drug administration such that there was at least 8 hours supervised fasting before the scheduled dose of each treatment period and subjects remained housed in the clinical facility until the 8 hour post dose blood sample have drawn in each of the study periods.

The volunteers were divided into 2 groups of 6 members. After a supervised overnight fasting for at least 08.00 hours, subjects of first group were administered a single oral dose of the test product [Cureit Capsules 500mg] and the subjects of second group were administrated the reference product [Curcumin Capsules 500 mg]. After 14 days of washout period, the first group of subjects consumed the reference product, and the second group of subjects consumed the test product. Subjects remained seated upright for first four hours after dosing. Thereafter they were allowed to engage in normal activities avoiding severe physical activities. The pre-dose sample was collected within 1 hour prior to drug administration. The post-dose blood samples were collected at 1.00, 2.00, 3.00, 4.00, 5.00, 6.00 and 8.00 hours in each study period. The blood samples were collected for each volunteer in pre-specified vacuum tubes containing anti-coagulant. The Plasma was separated from the blood samples, and kept frozen until analyzed.

Extraction and chromatographic analysis of Curcumin from Plasma:

Each sample of plasma was taken and allowed to attain room temparature, and was extracted with ethyl acetate (3+2 ml). The extracts of each sample were pooled and filtered into evaporation tubes. The solvent was evaporated under the stream of nitrogen gas, in fumehood. Added 1 ml of methanol to redissolve the dried sample. Vortexed the sample, and taken an aliquot from this, and analysed using UHPLC, Shimadzu.

Analytical conditions:

Analysis for Curcumin have carried out in UHPLC (Shimadzu, NEXERA, model LC30 AD). The column used was 2mm*150mm, shim pack,XR-ODS III. An isocratic elution was used with mobile phase of composition 40% THF and 60% water containing 1% citric acid at a flow rate of 0.5ml/ min. Under identical conditions, a six point linearity curve was plotted using standard Curcumin of 97% purity, in a range of 2ng/ml-500ng/ml.

RESULTS AND DISCUSSION:

Curcumin is a safe, effective and potential compound, finds its application as an ingredient for foods and medicines. In order to be effective as a medicine, it has to be more bio available than usual forms. Even though the concentration by composition is increased, it cannot be absorbed to the body- but, some formulations can.

A method was validated with Curcumin standard, and content of Curcumin in the blood plasma were quantified. Curcumin peaks (C1, C2 and C3) are identified using reference standard. Curcumin content in serum was calculated and the results are expressed as ng/ml serum.

The current study results are tabulated and given below (Tables 1, 2 and 3). Table 1 gives the time profile for the plasma concentration of Curcumin with the reference sample. Table 2 gives the time profile for the plasma concentration of Curcumin with the test sample- cureit. For both the samples, the absorption trend remains the same. The absorption of Curcumin is increasing gradually in the successive hours, after the consumption of the sample. It attains a maximum- for the test sample, the maximum is obtained at 4th or 5th hour and for the reference sample, the maximum absorption attained at 3rd or 4th hour- and then decreases gradually.

Absorption of Curcumin to plasma depends on the subjects also. In case of test sample, in the 1st hour, subject 2 shows a 93.7ng/ml concentration, while subject 5 possesses a concentration of 11.54ng/ml only. In the 4th hour, subject1 possess maximum plasma absorption of 654.34ng/ml, while in the 5th hour, subject7 shows the maximum observed absorption of 931ng/ml. In case of the reference sample, in the 1st hour, subject12 shows absorption of 34.23ng/ml, while subject 9 shows an

absorption of 5.9ng/ml only. The maximum observed absorption for the reference sample is for the subject7, at 3rd hour- 61.2ng/ml.

Table 1: Plasma Concentration (ng/mL) Vs Time Point (hrs) of Reference Formulation -Curcumin-95% in 12 healthy adult, male, human Subjects.

Subject No.	Time Point (hr)							
	0	1	2	3	4	5	6	8
2	2.2	22.5	37.6	45.04	35.67	23.05	19.88	6.5
3	2.1	28.57	40.78	42	52	20.2	16.64	0.79
4	2.9	15.4	17.69	35.6	47.61	22.09	19.4	4.5
5	2.2	9.24	13.75	27.25	49	20.44	14.1	1.1 15
6	1.8	17.56	35	37	41	21	15.82	0.8
7	1.8	14.4	18.2	61.2	29.4	19.8	15.32	5.8
8	2.7	12	26	27.9	21.9	21.71	19.7	2.2
9	3.089	5.9	8.3	17.47	6.02	5.9	6.81	0
10	2.7	17.92	24.52	31.8	37.17	14.22	15.92	1.45
11	2.5	16.76	16.86	19.3	22.48	11.66	10.2	5.22
12	2.5	34.23	31.9	39.1	32.4	13.29	10.07	0.96
Mean	2.43	23.52	25.4	35.5	35.7	22.621	15.68	3.6
SD	0.41474	20.32995	10.5753	12.0294	14.3169	18.3427	4.91517	2.6585

Table 2: Plasma Concentration (ng/mL) Vs Time Point (hrs) of Test Formulation- cureit, in 12 healthy adult, male, human Subjects

Subject No.	Time Point (hr)							
	0	1	2	3	4	5	6	8
1	3.5	16.77	69.22	492.9	654.34	47.99	42.18	2.6
2	1.9	93.7	124.49	144.96	329.7	117.2	77.47	5.9
3	2.1	42.6	62.44	490	320.19	89.05	43.78	5.06
4	1.8	29.79	246.3	201	263.5	304	33.2	0
5	2.6	11.54	13.6	40.9	114.5	281.9	11.15	2.28
6	2.9	15.82	17.7	122.6	552.16	425.9	9.75	0.8
7	2.9	27.18	28.39	34.86	505.43	931	183.38	5.8
8	2.6	20.9	26.7	48.63	327	582	92.35	3.24
9	2.013	37.9	48.3	80	285.69	40.8	37	2.2
10	2.9	23.83	27.07	40.81	193.9	54.34	28.69	5.22
11	2.7	22.14	34.32	49.88	270.1	37.17	30.9	0
12	2.1	25.29	38.2	47	104.01	75.85	30.6	1.3
Mean	2.5	30.6	61.39	149.46	326.71	248.9	51.7	3.44
SD	0.495	21.75	65.602	167.724	168.229	278.121	47.843	1.854

Table 3: Pharmacokinetic values

Parameters	Means ± SD	
	Test (T)	Reference (R)
Cmax (ng/mL)	434.25±256.605	43.1±16.733
AUCo-t (ng x hr/mL)	904±459.725	165.7±55.759
AUC o-inf (ng x hr/mL)	980±508.104	192.8±63.886
Tmax (hrs)	4.2±0.621	3.6±0.651
T1/2 (hrs)	2.04±0.310	1.8±0.325

The results show that, "cureit" possesses a good bioavailability, comparing to Curcumin 95% standard. The results of this study prove that the bioavailability as measured by the Cmax as well as AUC of cureit was 10-fold more, compared to Curcumin 95%.

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