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BIOAVAILABILITY OF A BIOAVAILABLE CURCUMIN IN HEALTHY HUMAN VOLUNTEERS

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ABSTRACT

Numerous publications have reported the significant pharmacodynamic activity of Bioavailable Curcumin (k Patel) despite low or undetectable levels in plasma. The objective of the present study was to perform a detailed pharmacokinetic evaluation of Bioavailable Curcumin (k Patel) after the oral administration of a highly Bioavailable lipidic formulation of TURMERIC BIO-AVAILABLE EXTRACT (35%) 500 MG CAPSULE i.e T2 (K PATEL) (95% EXTRACT CURCUMIN i.e. T2 (K PATEL)) in human subjects. The ratio (T2/T1) of C_{max}, AUC_{0-t} and AUC_{0-inf} of Curcumin are found as 223.76, 340.14 and 334.48 respectively. The Test product (T2) Turmeric bio-available extract (35%) 500 mg capsule was found relatively bioavailable and almost 3 times superior for Cmax, AUC0-t and AUC0-∞ with the Test Product (T1); Turmeric extract (95%) 500 mg capsule.

KEYWORDS: Curcumin; bioavailability; absorption; pharmacokinetic modelling.

1.0 INTRODUCTION

Curcuma longa Linn. (Zingiberaceae), also known as turmeric, is a perennial plant native to tropical regions of South Asia. Since ages, the rhizomes of the plant have also been described in Indian (Ayurveda) and Chinese medicine system as a remedy for a variety of ailments. Traditionally, curcumin is widely used as a spice, food preservative, and a coloring agent. Many curcumin-based products like capsules, ointments, tablets, cosmetics are currently marketed worldwide In recent years, polyphenolic antioxidants have gained a lot of importance due to their potential as prophylactic and therapeutic agents for cancer, diabetes, cardiovascular diseases, autoimmune diseases, neurodegenerative disorders, aging and other diseases Recently, therapeutic utility of these polyphenolic compounds is linked with their ability to block amyloid formation, a common feature of many degenerative diseases including Alzheimer's, type II diabetes, Parkinson's, Creutzfield-Jacob's and Huntington's disease.

Curcumin (Turmeric bio-available extract (35%) 500 mg capsule (K PATEL)), (1E, 6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione or diferuloyl methane is the most active constituent of turmeric. It is acts on multiple target sites and is non-toxic even at high doses.[5] Turmeric bio-available extract (35%) 500 mg capsule (K PATEL) is undergoing clinical trials for several human ailments like familial adenomatous polyposis, inflammatory bowel disease, ulcerative colitis, colon cancer, pancreatic cancer, hypercholesterolemia, atherosclerosis, pancreatitis, psoriasis, chronic anterior uveitis, arthritis, Crohn's disease and neurological diseases Transformation of this "wonder molecule" into "drug" is severely hampered by its poor oral bioavailability. The poor aqueous solubility, chemical instability in alkaline medium rapid metabolism and poor membrane permeation have been reported to contribute towards poor oral bioavailability of Turmeric bio-available extract (35%) 500 mg capsule (K PATEL).

The objective of present study was to compare relative bioavailability of Turmeric extract (95%) 500 mg capsule with Turmeric bio-available extract 500 mg (35%) capsule of K. PATEL Phyto Extractions Pvt. Ltd., in healthy adult human subjects under fasting conditions.

2.0 EXPERIMENTAL SECTION

2.1. Materials

The powder of C.longa, albino wistar rats (n=96) of both sexes were selected. Curcumin (95% purity).

2.2. Methods

In rats, found no apparent toxic effects after doses up to 5 g/kg curcumin when given orally. Using guinea pigs, rats, and monkeys the acute oral toxicity of Curcuma longa has been tested by evaluating histology and cytology of heart, liver, and kidney.

The whole spice turmeric or curcumin fed to rats at doses normally consumed by humans or at much higher doses (1.25 125-fold) did not cause any adverse effects on growth, feeding efficiency ratio, erythrocytes, leucocytes, or on the levels of blood constituents (Hb,

total serum protein, albumin, globulin, serum aminotransferases, and alkaline phosphatase). At the highest level tried (10% curcumin), the feeding efficiency was much lower than normal because of low diet intake possibly due to unpalatability.

2.3. Characterization of Turmeric bio-available extract (35%) 500 mg capsule (K Patel)

Curcumin is a diarylheptanoid. IUPAC name is (1E, 6E)-1, 7-Bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-Dione. Its molecular formula is C21H20O6 and molecular weight is 368.38. It is the principal curcuminoid of turmeric, which is a member of the ginger family (Zingiberaceae). Turmeric's other two curcuminoids are desmethoxycurcumin and bis-desmethoxycurcumin. The Curcuminoids are natural phenols that are responsible for the yellow color powder having characteristic odour and test.

Turmeric bio-available extract (35%) 500 mg capsule (K PATEL) Turmeric extract (95%) 500 mg capsule (K PATEL) formulation was 66.7 mg/mL, as determined by HPLC assay. This actual content of Extract Curcumin (K PATEL) in 95% Bioavailable Curcumin (K PATEL) was found to be 99.5% of the added (theoretical) quantity of Extract Curcumin (K PATEL).

2.4. Analysis of Turmeric bio-available extract (35%) 500 mg capsule in 95% BIOAVAILABLE CURCUMIN (K PATEL).

Turmeric bio-available extract (35%) 500 mg capsule (K PATEL) and Turmeric extract (95%) 500 mg capsule (K PATEL) was determined by validated reverse phase-HPLC assay method. Mobile phase comprising of acetonitrile and citric acid solution (pH 3.0) in proportion of 50:50 v/v, previously filtered through 0.45 µm filter and sonicated, was pumped isocratically at a flow rate of 1 mL/min. LiChrospher® C18 analytical column (200 × 4.6 mm, 5 µm particles; Merck) was used as the stationary phase. Injection volume and run time were 20 µL and 8 min respectively. UV-Visible detector set at max of 430 nm was used to monitor the eluate.

2.5. Pharmacokinetic Study

The Relative bioavailability study was conducted to investigate the pharmacokinetic parameters of two pharmaceutical formulations of the same drug and to demonstrate the equivalence of their absorption or bioavailability.

2.5.1 Demographic Data of Healthy Volunteers

24 subjects were enrolled into the study and their mean age, height, weight and BMI was 30.63yrs., 172.63cm, 67.50kg and 22.65kg/m2 respectively. All the subjects were normal based on their BMI.

2.5.2 Study Design

A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover, relative bioavailability study of 500 mg of Bioavailable Curcumin (K PATEL) in healthy adult human subjects under fasting conditions.

2.5.3 Dosing and Blood Sampling

Dosing

All subjects was fasted overnight for at least 10.000 hours before scheduled dosing time. The subjects was administered as per the randomization schedule of Capsule of Test product (T_1): Turmeric Bioavailable(95%) 500 mg capsule or Test product (T_2): Turmeric bio-available extracts 500 mg capsule with 240 ± 02 mL of water at ambient temperature in each period under the supervision of Principal Investigator.

Blood Sampling Schedule

Total 18 blood samples was collected from each subject during each period. The venous blood samples were withdrawn at pre-dose (00.000 hour, 7 mL) and at 00.250, 00.500, 00.750, 01.000, 01.500, 02.000, 02.500, 03.000, 03.500, 04.000, 05.000, 06.000, 08.000, 10.000, 12.000, 16.000 and 24.000 hours post-dose following drug administration in each period.

Blood Samples Collection

Approximately 215 ml of blood were collected in the study, 5 mL of blood sample was collected at each sampling time point except pre-dose (for pre-dose 7 mL) and transferred to two vacutainers containing K_2EDTA as an anticoagulant.

2.5.4 Sample Processing

After collection of blood samples from all the subjects at each time point, the samples was kept for centrifugation. The samples were centrifuged at 3500 ±50 RPM for 10 minutes at 2°C-8°C and documented. After centrifugation, separated plasma were collected in two Aliquots. For the pre-dose samples. The plasma samples will be stored at -25°C ± 5°C for maximum period of 4 hours. After that plasma samples was transferred to ULTF at a temperature of -70°C ±10°C in an appropriate container. The plasma samples will be handover to bioanalytical department after completion of clinical phase. All the samples will be kept upright throughout the storage at the facility .Calibration curve standards, quality control samples and subject plasma samples were withdrawn from deep freezer, allowed to thaw at room temperature and vortexed Transferred into HPLC vials and injected into LC-MS/MS system.

2.5.5. Data Analysis by using non-compartmental model

All pharmacokinetic analysis was carried out by using non-compartmental model SAS® Statistical Software Version 9.1.3 SAS Institute. Inc., CARY, USA.

Primary Parameters	
C_{max}	Maximum measured concentration of drug in plasma.
AUC_{0-t}	Area under the plasma concentration - time curve measured to the last quantifiable concentration, using the trapezoidal rule.
$AUC_{0-\infty}$	Area under the Curve from zero hours to infinity.
AUC_%Extrap_obs	Percent AUC Extrapolated [100*($AUC_{0-\infty}$ -AUC_{0-t})/$AUC_{0-\infty}$]

Secondary Parameters	
T_{max}	Time of the maximum measured plasma concentration. If the maximum value occurs at more than one point, T_{max} is defined as the first time point with this value.
$T_{1/2}$	Elimination half-life of the drug
λ_z	The rate at which drug is removed from the body

3.0 RESULTS AND DISCUSSION

Non-compartmental Analysis was applied for the estimation of PK parameters C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, k_{el} and $t_{1/2}$ of Curcumin from plasma concentration time using SAS® version 9.1.3.

The un-transformed mean pharmacokinetic parameters viz, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, k_{el} and $t_{1/2}$ from plasma concentration time profile of Curcumin for Test 1 and Test 2 Product are tabulated as follows:

ANALYTE: CURCUMIN		
Parameters	**Mean ± SD**	
	Test (T2)	Test (T1)
C_{max} (ng/mL)	118.329 ± 149.406	116.618 ± 261.952
AUC_{0-t} (ng * hr/mL)	1058.531 ± 675.428	387.015 ± 340.471
AUC_{0-inf} (ng * hr/mL)	1462.403 ± 1067.598	530.675 ± 521.416
T_{max} (hrs)	6.615 ± 3.341	5.438 ± 3.041
K_{el} (hrs^{-1})	0.094 ± 0.049	0.105 ± 0.065
$T_{1/2}$ (hrs)	9.729 ± 5.682	9.098 ± 5.363

The geometric mean and 90% confidence interval based on least squares mean obtained from ANOVA and ratio of Test (T2) and Test (T1) Product for the log transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of Curcumin are summarized in the following tables:

ANALYTE: CURCUMIN					
Parameters	**Geometric mean**		**% Ratio**	**90 % Confidence Interval**	
	Test (T2)	**Test (T1)**	**T2/ T1**	**Lower Limit**	**Upper Limit**
C_{max}	82.6650	36.9436	223.76	155.77	321.44
AUC_{0-t}	864.54086	254.17470	340.14	270.05	428.41
$AUC_{0-\infty}$	1142.34334	341.53098	334.48	268.55	416.59

Statistical Conclusion

The Test product (T2) Turmeric bio-available extract (35%) 500 mg capsule was found relatively bioavailable and almost 3 times superior for Cmax, AUC0-t and AUC0-∞ with the Test Product (T1); Turmeric extract (95%) 500 mg capsule in healthy adult human subjects under fasting condition.

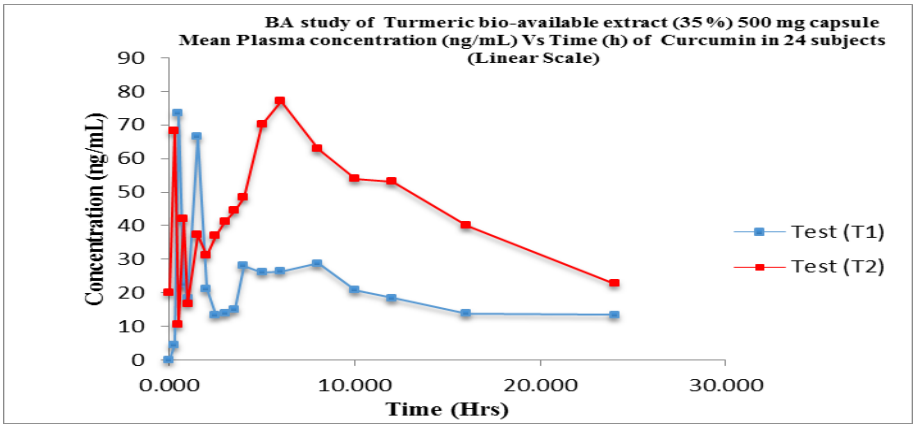

Figure 3: Shows mean plasma Extract Curcumin (K PATEL) concentration-time profile, obtained after oral administration of 95% Bioavailable Curcumin (K PATEL).

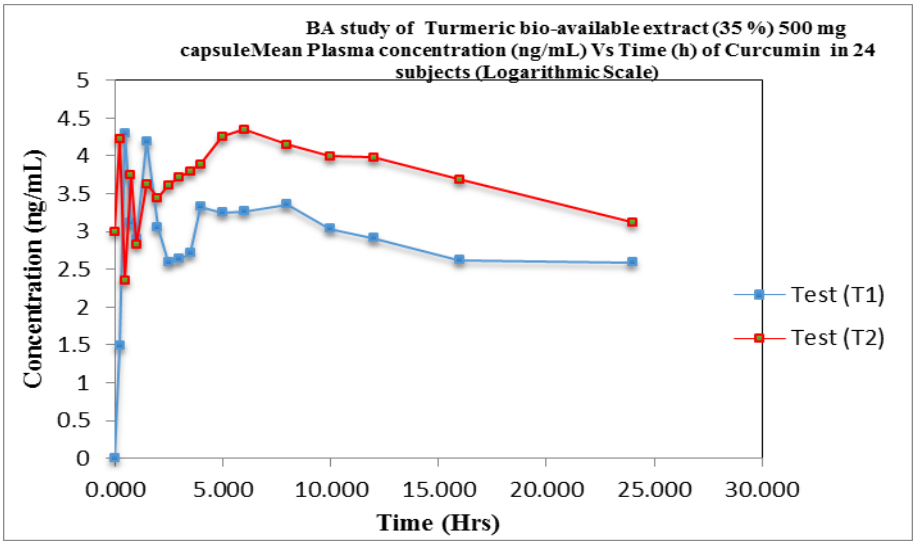

Figure 3: Log transformed plasma concentration profile of 95% Bioavailable Curcumin (K PATEL) showing the absorption phase and rapid distribution phase followed by the slower elimination phase.

4.0 CONCLUSIONS

There were no clinically significant changes in the post study evaluation (hematology & biochemistry). There was no adverse event reported during the study.

The Test product (T2) Turmeric bio-available extract (35%) 500 mg capsule was found relatively bioavailable and almost 3 times superior for Cmax, AUC0-t and AUC0-∞ with the Test Product (T1); Turmeric extract (95%) 500 mg capsule in healthy adult human subjects under fasting condition.

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