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Original Research Article

Bioavailability of curcumin from a novel mouth dissolving lozenge

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ABSTRACT

Background: Cucurmin is the main component of curcuminoids in turmeric (*Curcuma longa*). Turmeric, popularly used as food colourant, is traditionally used as a medicinal herb owing to its antioxidant, anti-inflammatory, antimicrobial and anticancer properties. The gastric absorption of curcumin is poor and therefore various forms like encapsulation in liposomes, polymeric nanoparticles, cyclodextrin encapsulation, lipid complexes, polymer-curcumin complex etc. have been evaluated.

Methods: In the current study, a novel lozenge of 100mg turmeric extract in mouth dissolving formulation is evaluated for bioavailability of curcumin as compared with the conventional hard gelatin capsule containing 475mg curcumin. Fourteen healthy male subjects of Indian origin are dosed in a two way, two treatments, two sequence cross-over balanced, randomized design. Blood samples are collected sequentially to cover the plasma concentration-time curve to obtain a reliable estimate of the extent of absorption. Blood plasma is processed and analyzed using a validated isocratic HPLC-MS/MS method to estimate the concentration of curcumin.

Results: Curcumin is detected at m/z 369→177, while the internal standard diazepam is detected as m/z 285→193 to quantify curcumin. Results indicate a significant increase in bioavailability of curcumin from the lozenge (C_{max} 188.863±22.9620ng/ml; AUC_{0-t} 897.026±65.4844ng/mL*hr) as compared to the hard gelatin capsule (C_{max} 96.458±15.8272ng/ml; AUC_{0-t} 440.744±77.3470ng/ml*hr).

Conclusions: Mouth dissolving lozenge could be a pragmatic approach to circumvent the low bioavailability of curcumin from therapeutic formulations.

Keywords: Bioavailability, Cucurmin lozenge, LC-MS/MS, Turmeric

INTRODUCTION

Curcumin (1,7 - bis (4-hydroxyl-3 -methoxypheny1)- 1,6 - heptadiene - 3,5-dione) also called diferuloylmethane, is the main natural polyphenol found in turmeric (rhizome of *Curcuma longa)*.[1] Curcumin is a crystalline compound with a bright orange-yellow colour and is popularly used as food colorant.[2] It is a keto-enol tautomeric compound existing predominantly in the keto-form in acid or neutral solutions and in the enol-form in alkaline solutions.[3] Curcumin is soluble in alkali or in extremely acidic solvents.[4] Different activities have been directly associated according to the keto or enol forms of curcumin.[5] Turmeric is traditionally used in Asian countries as a medical herb for its antioxidant, anti-inflammatory, antimutagenic, antimicrobial, and anticancer properties [2,6-9]

Besides curcumin, there are others curcuminoids in *Curcuma longa*; demethoxycurcumin and bis-demethoxycurcumin. Curcumin, however, is the most abundant of all curcuminoids. Curcuminoids form around 5% of the total component of *Curcuma longa*.[10] It has been

reported that the bioactivity of *Curcuma longa* is due to the synergistic action of the curcuminoids, for example the nematocidal acitivity.[11] Curcumin is an antioxidant and also increases the activity of detoxifying enzymes both in liver and kidneys.[12-14] Curcumin is an anti-inflammatory and antioxidant compound possessing anti-rheumatic and anti-arthritic properties.[15-18] It provides health benefits mainly through anti-inflammatory and antioxidant mechanisms.[19]

In the last decade, many experimental studies on *in vivo* and *in vitro* models have been reported for discerning the mechanisms of bioactivity of curcumin and its activities against several pathologies.[20] curcumin administered orally in patients with colorectal cancer showed no toxic effect. Curcumin was mainly detected as curcumin glucuronide and curcumin sulphate post administration.[21] Studies with labeled (3H)-curcumin in rats, have showed the difficult intestinal absorption of curcumin and the biotransformation of curcumin to its glucuronides; tetrahydrocurcumin and hexahydrocurcumin derivatives.[22] Curcumin is reported to be first transformed to dihydrocurcumin and tetrahydrocurcumin by reductases and then transformed into dihydrocurcumin-glucuronide and tetrahydrocurcmin-glucuronide by β-glucuronidase.[23]

For improvement its bioavailability, curcumin in various forms like encapsulation in liposomes, polymeric nanoparticles, cyclodextrin encapsulation, lipid complexes or polymer-curcumin complex have been evaluated. All of them have helped in increasing the bioavailability of curcumin to varying extend.[24] Transformed curcumin have also been demonstrated to improve the beneficial effect of curcumin in cancer management and in management of liver diseases.[25,26]

Conventional dosage forms of curcumin consist of oral hard gelatin capsules and liquids, which do not bypass the gastric metabolism. The current study therefore, evaluates an alternate route that can bypass the gastric metabolism. Mouth-dissolving lozenges of curcumin developed [redacted] India are evaluated for the bioavailability of curcumin. This paper reports the results of the bioavailability study conducted with the mouth-dissolving turmeric lozenges as compared with the conventional hard gelatin capsules of curcumin. Ancient Ayurvedic texts provide evidence that highly lipophilic bioactive compounds when administered in vehicles with fatty base like milk, ghee etc., improve their solubility and permeation through tissues. Several Ayurvedic drugs are co-administered with plant drugs containing phytochemicals like piperine which have been reported to improve bioavailability.[27] Thus, the buccal lozenge is designed with a delivery system that can help solubilize curcumin. The base formula of the lozenge is patented and the innovator was able to develop a mouth dissolving pastille. The state of art technology helped to develop this lozenge helps to maintain the stability of the phytoflavonoids and curcuminoids intact in the soft pastilles. The product is supplied in blister and has 3 years shelf life at room temperature.

The formulation has been designed as a delivery system for curcumin which would also prevent its biotransformation and its inactivation by the liver enzymes. The study therefore, estimates the blood levels of curcumin post-administration of the buccal lozenge and compare it with that of the conventional hard gelatin capsule as the reference formulation. The comparative bioavailability study was designed with two main evaluable objectives; (i) estimating buccal absorption of curcumin through the patented lozenge formulation and (ii) estimating the level of plasma curcumin (non-conjugated) after the administration of the lozenge and compare it with that from the conventional hard gelatin capsules.

The current study is designed as an open label, balanced, randomized, two periods, two sequence single dose, crossover bioavailability study of turmeric Lozenges containing 100mg turmeric extract per lozenge and curcumin hard gelatin capsule containing 475mg curcumin per capsule in twelve healthy, adult, male human subjects of Indian origin under fasting condition. Fourteen volunteers were enrolled to obtain twelve completed subjects. The study is duly approved by the Institutional Ethics Committee (Approval No. TL 160922-01 of 3rd November 2016).

METHODS

Investigational products

The TEST product is [redacted] manufactured by [redacted]. with each lozenge containing 100mg turmeric extract. The REFERENCE product is turmeric hard gel capsule manufactured by West-Coast Pharmaceuticals Works Ltd. Gujarat (India) with each capsule containing 475mg curcumin per capsule.

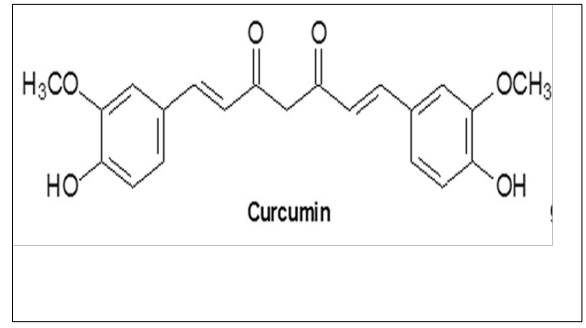

Figure 1: Structure of curcumin.

Reagents and chemicals

Pure standards of curcumin ($C_{21}H_{20}O_6$) (purity >89.49%) were procured from the [redacted]

Ltd. The chemical structure of curcumin is illustrated in Figure 1. Methanol, Acetonitrile (HPLC grade), Formic acid (AR grade), tert-methyl butyl ether and ammonium acetate were purchased from Merck Ltd., Mumbai, India. Ultra-pure (Milli-Q) water of 18.2MΩ resistances and 0.22µ membrane filtered was obtained from Millipore water purification system (Molsheim, France). β-glucuronidase was purchased from Sigma Aldrich. All other chemicals used in the study were of analytical reagent (AR) grade.

Instrumentation and chromatographic conditions

Apparatus and instruments

The Perkin Elmer HPLC system (Perkin Elmer, Norwalk, CT, USA) used consists of a PE Series 200 pump, an autosampler with a peltier-thermostated tray and a vacuum degasser. The HPLC system is interfaced with an Applied Biosystems Hybrid Q-Trap API 2000 mass spectrometer (AB-MDS Sciex, Toronto, Canada) equipped with an ESI source by analyst 1.3 data acquisition and analysis software (AB Sciex, USA).

HPLC-MS/MS Conditions

Chromatographic separation is carried out on a Cosmosil C_{18} column (150 x 4.6mm, i.d.; 5µm particle size) from Nacalai Tesque, Kyoto, Japan. The mobile phase consisted of solvent Acetonitrile: 0.1% Formic acid (60:40, *v/v*). The flow rate of the mobile phase was 1.0 mL/min with a split ratio 1:4 (MS:Waste). The run time was 10 min/sample. The flushing solvent used was acetonitrile: water (1:1, *v/v*). The auto-sampler temperature was set to 8°C±2°C.

The bioanalytical method was developed based on earlier reports with appropriate modifications.[28,29] An LC system consisting of an electrospray ionization tandem mass spectrometer (ESI-MS/MS) was used. ESI-MS/MS is performed in the positive mode. Multiple-reaction monitoring, using the precursor → product combination of m/z 369 →177, m/z 285 →193 was used to quantify curcumin, and the internal standard (Diazepam) respectively (Figure 2 and 3).

The ESI source was operated in the positive ionization mode. De-clustering Potential (DP), Entrance Potential (EP), Collision Entrance Potential (CEP), Collision Energy (CE), Collision Exit Potential (CXP) were set to 40V, 5V, 22V, 15eV and 5V respectively for curcumin and 45V, 10V, 22V, 20eV and 8V respectively for Diazepam. Curtain gas (CUR), Ion Spray Voltage (ISP), Nebulizer gas (GS1) and Heater gas (GS2) were set at 15 psi, 5500V, 30 psi and 70 psi respectively for curcumin and IS. The ion source temperature was maintained at 250°C. The mass spectrometer quadrupoles were operated in the unit resolution model; while CAD gas was set to medium. Dwell time for both the transitions was set to 200ms.

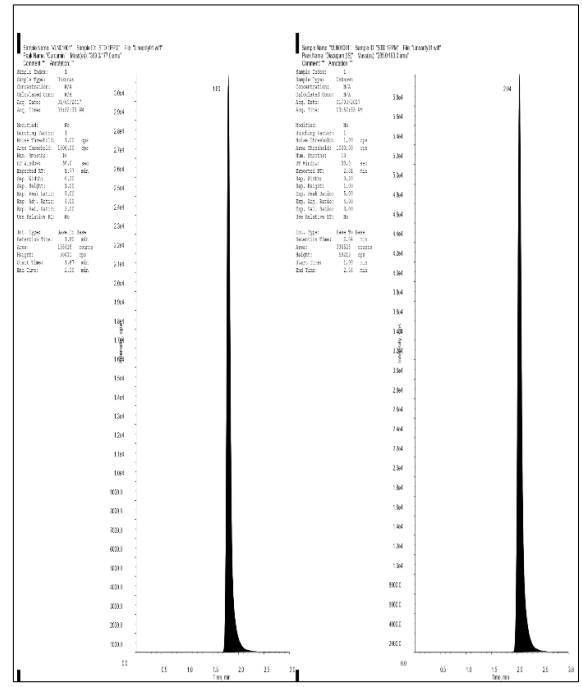

Figure 2: LC-MS/MS chromatogram for curcumin (1ppm standard) and IS diazepam (1ppm standard).

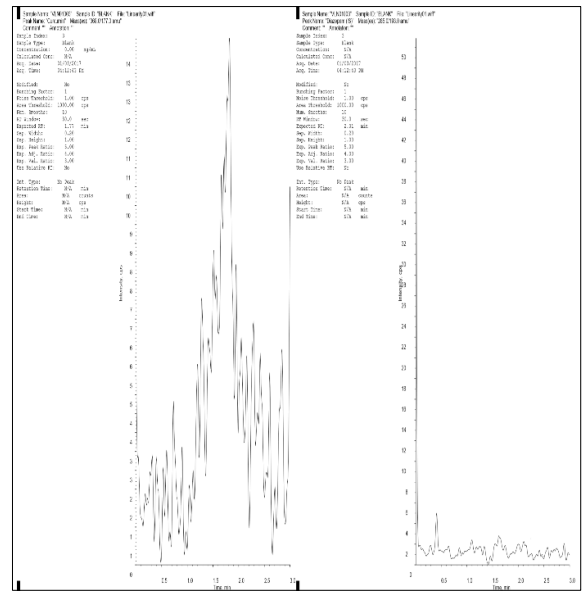

Figure 3: LC-MS/MS chromatogram for blood plasma showing no interference at RT of curcumin and diazapam.

Preparation of stock and working standard (calibration standard) solutions

Curcumin stock solution (1000ppm) is prepared in Acetonitrile: Ammonium acetate buffer (pH 4.5, 0.1M, 50:50*v/v*). Diazepam stock solution (1000ppm) is prepared in Methanol. The diluent used is 0.1% formic acid:

Acetonitrile (1:1*v/v*) for curcumin and IS to prepare, 100ppm, 10ppm, 1ppm working stock solutions. From standard stock solutions, concentrations of 10, 20, 50, 100, 200, 300, 400, and 600ng/ml are prepared by diluting previously prepared solution up to 10ml with diluent volume in separate 10ml volumetric flasks.

Sample preparation

The frozen plasma samples are thawed at room temperature, vortexed for 2 minutes prior to analysis. 100µl of phosphate buffer solution (75mM; pH 6.8) with 1000U β- glucuronidase is added to 500µl of plasma is aliquoted. The resulting solution is incubated at 37 °C for 1 hour to hydrolyse the curcumin conjugates. Following hydrolysis, the samples are spiked with 100µl of 0.1M ammonium acetate buffer (pH 4.5) and 20µl of IS working standard solution. The mixture is then extracted with tert-methyl butyl ether (5ml) by rotary shaker followed by centrifugation at 3000 rpm. The clear supernatant is evaporated under a stream of nitrogen at 40°C until dryness. The dried residue is reconstituted in 100µl mobile phase. The reconstituted samples are vortexed for 1 minute and 10µl of the supernatant is injected into the LC-MS/MS system.

Clinical study

Overall the study is designed for participation of both male and female subjects, but only male subjects showed willingness to participate in the study. The subjects are screened and 14 healthy subjects of age between 18 and 45 years (both inclusive) are selected by obtaining demographic data (Age, Height, Weight and BMI), clinical examination (physical and systemic examination) including vital signs, complete medical history, conducting clinical laboratory tests (Haematology, Biochemistry, Serology and Urine analysis), ECG recordings. Treatments are allocated to subjects by carrying out randomization using the SAS software. Subjects reported to the study site the evening prior to the day of dosing and are confined at the study centre for 24 hours post dose. Each subject provided a written consent to be part of the study. The total duration of clinical phase of the study is 12 days with 8 days of wash between two periods. The study period started with check-in of subjects for period one on 7th December 2016 and ended with the last blood sample withdrawn during period two on 18th December 2016. At check-in to the study centre, Salivary alcohol Test, Screening Test for Drugs of Abuse (in urine sample) are performed on the day of check-in of each period of the study. Blood samples are drawn before dosing and up to 48.00 hours after dosing. Subjects are instructed during screening to refrain from smoking, chewing tobacco, or use products containing beetle nut and / or tobacco and from consuming any alcoholic products, xanthine-containing foods or beverages (like chocolate, tea, coffee or cola drinks), grapefruit juice and citrus fruit for 48 hours prior to dosing till the completion of study.

The subjects selected for study participation are those who met the inclusion criteria of age between 18 and 45 years, Body Mass Index between 18.5kg/m^2 to 24.9kg/m^2, body weight between 50.00-80.00Kg, normal health as determined by personal medical history, clinical examination and laboratory examinations within the clinically acceptable normal range, normal 12-lead electrocardiogram, negative urine screen for drugs of abuse (including amphetamines, barbiturates, benzodiazepines, marijuana, cocaine, and morphine), agree to avoid tobacco products, xanthine containing products (chocolate, tea, coffee, cola drink), grapefruit etc., willingness to adhere to the protocol requirements and to provide written informed consent, no known history of contraindication and / or allergy to turmeric, not consumed medical drugs for two weeks prior to the study and not participated in any clinical study at least 3 months prior to the current study.

The subjects who meet any of the exclusion criteria are excluded. The exclusion criteria includes known hypersensitivity to curcumin or any inactive ingredients in the formulation, history or presence of significant cardiovascular, pulmonary, hepatic, renal, gastrointestinal, endocrine, immunological, dermatological, neurological or psychiatric disease or disorder, undergone any treatment which could bring about induction or inhibition of hepatic microsomal enzyme system within 1 month before the current study, history or presence of significant alcoholism or drug abuse in the past one year from the commencement of the current study, history or presence of significant smoking (more than 10 cigarettes per day or consumption of tobacco products, history or presence of significant asthma, urticaria or other allergic reactions, history or presence of significant gastric and/or duodenal ulceration, history or presence of significant thyroid disease, adrenal dysfunction, organic intracranial lesion such as pituitary tumor, history or presence of cancer, difficulty with donating blood, difficulty in swallowing solids like tablets or capsules, presence of disease markers of HIV 1 or 2, Hepatitis B or C viruses and syphilis, systolic blood pressure less than 100mmHg or more than 140mmHg, diastolic blood pressure less than 60mmHg or more than 90mmHg, pulse rate less than 60/minute or more than 100/minute, oral temperature less than 35°C or more than 37.5°C, respiratory rate less than 12/minute or more than 20/minute, use of any prescribed medication during last two weeks or OTC medicinal products (during last one week) and grapefruit juice during the last 48 hour prior to initiation of study, major illness during 3 months before screening, participation in a drug research study within past 3 months, donated blood in the past 3 months before screening for the current study or have been on a medically prescribed special diet (e.g., low sodium) for two weeks prior to the current study.

Subjects are provided with turmeric free food from the dinner of the evening before dosing till check out in both treatment periods. The subjects are fasted overnight for at least 10 hours before dosing. Investigational product (One

Lozenge) is administered in sitting posture by placing the Lozenge either on the right or left cheek inside the mouth as per randomization. The subject is asked to keep Lozenge at the cheek site for 10 minutes without chewing after which the inside of cheek area is checked for complete dissolution of Lozenge. If the Lozenge is not dissolved, the cheek site is checked every one minute subsequently, till the Lozenge is completely dissolved. The time required for dissolution of Lozenge is noted for each subject. Investigational product (One hard gelatin Capsule) is administered in sitting posture along with 240ml of water. The subject is instructed to swallow the capsule with the water provided. The mouth cavity of the subject is checked to ensure complete swallowing. The dosing either of the lozenge or the capsule is made as per the randomization such that each volunteer received one of the treatments at each period of the study.

Subjects are provided standardized meals at about 4.00, 8.00 and 12.00 hours after dosing during both periods. Drinking water is not allowed from one hour before dosing till one-hour post-dose. Before and after that, drinking water is allowed at all times. Total duration of the study was 12 days from the day of check-in of the first period till the end of the second period. For monitoring the safety of subjects, their vital signs and well-being are recorded before dosing of Investigational Products (in the morning of the day of dosing) and at 2.0, 4.0, 8.0, 12.0 and 24.0 (±30 minutes) hrs. and 48 hours (±2 hours) post dosing. Upon entering into the study site, subjects are confined in the clinical facility to ensure 10 hours overnight fasting before dosing till 24 hours post-dose sample collection in each of the two periods. A washout interval of 08 days is kept between each consecutive dosing periods.

Sampling schedule is planned to provide an adequate estimation of C_{max} and to cover the plasma concentration-time curve long enough to provide a reliable estimate of the extent of absorption. Pre-dose blood sample of 5.0ml (0.00 hr) is collected within one hour prior to the dosing. Post-dose blood samples of 5.0 mL each are drawn at 0.25, 0.5, 0.75, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 24.00, and 48.00 hours following drug administrations in each period. For all the blood samples, the plasma obtained after centrifugation are aliquoted into two pre-labelled vials for storage. Vials are directly stored in bioanalytical facility at -70 ºC±5 ºC until analysis. A total of fourteen subjects are enrolled in the study; and thirteen subjects completed both the periods of the study and have been considered for Pharmacokinetic and Statistical analysis.

A validated LC-MS/MS bio-analytical method developed for the quantification of Curcumin in plasma is employed for sample analysis. A calibration curve extending over the range from 1.000ng/ml to 600.000ng/ml with a LLOQ of 1.000ng/ml for curcumin was used in subject sample analysis. Curcumin is detected with no interfering peak in all subjected who completed the study. The representative chromatograms from a single subject for blood samples withdrawn at 0.00hr. and 3.00 hr. is provided (Figure 4 and 5).

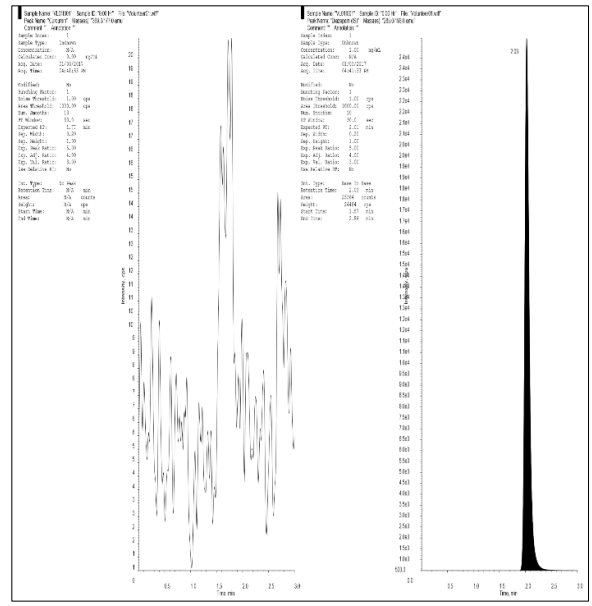

Figure 4: Representative LC-MS/MS chromatogram for blood plasma from subject at 0.00 hr. showing no detection at RT of curcumin.

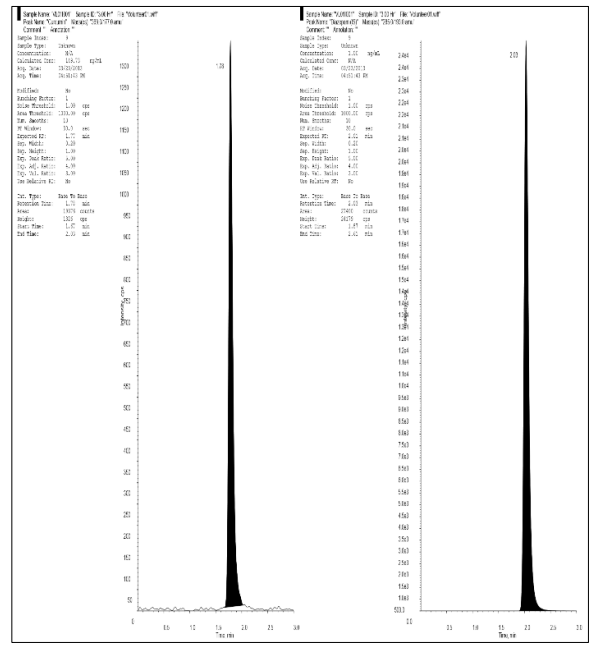

Figure. 5. Representative LC-MS/MS chromatogram for blood plasma from subject at 3.00 hr. showing significant detection of curcumin.

Statistical evaluation

For statistical analysis dataset for estimation of pharmacokinetic parameters T_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$,

$t_{1/2}$ and K_{el} for Curcumin are calculated using non-compartmental model by using WinNonlin® Enterprise Software Version 3.1 (Pharsight Corporation USA). The statistical comparison of the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Curcumin is also carried out using SAS® Version 8.2 (SAS Institute Inc., USA). A separate ANOVA model is used to analyze each of the parameters. The sequence effect is tested at the 0.05 level of significance using the subjects nested within sequence mean square from the ANOVA as the error term. All other main effects like period and treatment are tested at the 0.05 level of significance against the residual error (mean square error/MSE) from the ANOVA as the error term. The above analyses were carried out using PROC GLM in SAS Version 8.2. Geometric least square means of pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are computed and reported for Curcumin. Ratio of geometric least squares means are calculated and reported for parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Curcumin. For Curcumin, two-one sided 90% Confidence Intervals for the geometric least square mean ratio (T/R) obtained from the analysis of ln-transformed parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, are constructed using root mean square error computed by PROC GLM. Intra-subject variability and power are calculated and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ using root mean square error computed by PROC GLM for Curcumin.

RESULTS

Thirteen subjects completed the study while one subject withdrew due to personal reasons. No adverse events are recorded during the study. The test and reference products of curcumin were well tolerated by the subjects. No significant adverse events or serious adverse event occurred during the conduct of the study. The blood samples collected from 13 subjects are processed and analyzed for estimating the total curcumin. The pharmacokinetic parameters derived from the plasma concentrations of curcumin for each subject are provided in Table 1.

For curcumin, sequence effect, subject (Sequence) and period effects for ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were statistically insignificant, whereas treatment effect for ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were statistically significant. For curcumin, the two one-sided 90% confidence interval for the ratios of the log-transformed means is found to be 179.404% -219.828%. The median (min-max) T_{max} for reference and test formulations are 2.50 (2.50- 3.50) hours and 2.00 (1.50-2.50) hours respectively. The two one-sided 90% confidence interval for the ratios of the log-transformed means is found to be 183.541% - 227.182% while the two one-sided 90% confidence interval for the ratios of the log-transformed means is found to be 167.454% - 211.694%.

The C_{max} of Test formulation is significantly higher than the Reference formulation. AUC_{0-t} and $AUC_{0-\infty}$ of the test formulation is found to be significantly higher than Reference formulation. The T_{max} of Test formulation is earlier than the T_{max} of the Reference formulation. There is no significant difference in the K_{el} of Curcumin from the Reference and Test formulations. The $t_{½}$ of the curcumin from the test formulations is higher than the reference formulation indicating that curcumin remains in circulation longer when administered after test formulation. Being a Lozenge, the test formulation shows variability in the response of subject to the treatment of Lonzenge in the mouth. The intra subject variability is more than 10% CV.

Table 1: Pharmacokinetic parameters obtained for the turmeric hard gel capsule containing 475mg curcumin per capsule (Reference Product) and the Turmgel Lozenge containing 100mg turmeric extract (Test Product).

Parameters (Units)	Mean±SD (N = 13)	
	Reference product (R)	Test product (T)
C_{max} (ng/mL)	96.458±15.8272	188.863±22.9620
AUC_{0-t} (ng/ml*hr)	440.744±7.3470	897.026±65.4844
$AUC_{0-\infty}$ (ng/ml*hr)	512.321±97.0619	956.529±76.1716
*T_{max} (hr)	2.50 (2.50- 0.50)	2.00 (1.50-2.50)
K_{el} (1/hr)	0.17270± .11784	0.09048±0.03954
$t_{½}$ (hr)	6.25915±4.56349	9.15017±4.12146
*T_{max} expressed as median (min - max)		

DISCUSSION

Curcumin is a secondary metabolite of curcuma species with medicinal properties and is used as a dietary supplement. Several pharmacokinetic studies of oral curcumin have reported the glucuronides and sulfates of curcumin as the major molecules in the systemic circulation with trace concentrations of parent form of curcumin.[30] Due to their hydrophobicity, poor solubility in the chyme and instability at alkaline pH, only a small fraction of ingested curcuminoids is absorbed. In the intestine and liver, curcuminoids undergo rapid reduction to metabolites that are conjugated predominantly with glucuronic acid and are mainly excreted via the bile and urine.[27] A frequently employed strategy to improve bioavailability of curcumin is to administer curcumin in the form of novel delivery systems, such as nanoparticles, liposomes, or micelles, designed to enhance its solubility and stability in the gastrointestinal tract.[31] A significant increase of bioavailability of curcumin has been reported with 410mg micellar curcumin in human with 185-fold larger AUC and a 455-fold higher C_{max}.[32] In the current study, curcumin in oral dispersible lozenge containing 100mg curcumin has been evaluated for its bioavailability of curcumin. This dose of curcumin in lozenge is one-fifth of the conventional oral curcumin capsule of 500mg. The buccal absorption via the lozenge shall bypass the gastric

route and with no first pass effect, the low dose could deliver therapeutic levels of curcumin. Currently, the oral dosage forms of curcumin range from 500mg to 3000mg per day.

In the current study, administration of 475mg curcumin with hard gelatin capsule resulted in a C_{max} of 96.458±15.8272ng/ml which is in accordance with earlier reported work.[27] Administration of 100mg of curcumin with lozenge results in almost a 2-fold increase C_{max} as compared to that achieved with hard gelatin capsule. The AUC_{0-t} also shows a significant increase after administration of curcumin with the lozenge as compared to the hard gelatin capsule. It is interesting to note that the increased C_{max} is achieved after dosing at $1/5^{th}$ the conventional dose of 475mg given through hard gelatin capsule. This effectively reflects much better delivery of curcumin via the oral route of buccal absorption. Micellar formulation of curcumin containing curcumin 98mg provided an 88-fold increase in bioavailability.[27]

Curcumin is administered in divided doses up to 3000mg per day in the treatment of cancer where gastric irritation has been one of the most important deterrent side effect. The current study demonstrates the buccal absorption of curcumin with an innovative delivery system of lozenge which results in higher level of plasma curcumin level with 100mg dose compared to the 475mg of curcumin dosed through hard gelatin capsules. The absorption curve demonstrates that higher bioavailability is achieved with buccal lozenge, when the GI tract is by-passed. Buccal absorption, thus, is a better route especially, when local action in the buccal cavity is desired such as in dental infections, sore throat etc.

The current study demonstrates that 2-3 lozenges a day can result in therapeutic levels of curcumin for clinical benefits. The results will form the base line data for dose ranging studies and steady state concentration studies to establish complete pharmacokinetic parameters of the formulation.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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