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Research Article

Triple Fixed-dose combination of Dapagliflozin, Sitagliptin, and Metformin for People with Type 2 Diabetes in Indian Settings

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Abstract

Objective: This study assessed the bioequivalence of a fixed-dose combination (FDC) therapy containing extended-release Metformin (Metformin XR), Dapagliflozin, and Sitagliptin for treating type 2 diabetes (T2D). The objective was to compare the absorption rate and extent of the FDC with two reference products: Sitagliptin 100mg tablets (R1) and a combination of Dapagliflozin 10mg plus Metformin 1000mg extended-release tablets (R2) in healthy adult males under fed conditions.

Methods: An open-label, randomized, cross-over study was conducted with 24 healthy male participants. Each participant received a single dose of the test FDC and the reference products, with blood samples collected over 72 hours to evaluate pharmacokinetic parameters (Cmax, AUC0-t, AUC0-inf, Tmax, Kel, AUC_% Extrap_obs, and t1/2). Bioequivalence was determined based on the 90% confidence intervals (CIs) of the geometric mean ratios for AUC0-t and Cmax, within a predefined range of 80.00%-125.00%. Safety and tolerability were also assessed.

Results: Pharmacokinetic analysis was performed on 22 subjects. The geometric mean ratios for the FDC compared to the reference products were within the predefined bioequivalence range, indicating that the absorption profiles of the FDC and the reference products were similar. The mean plasma concentration-time curves for Dapagliflozin, Sitagliptin, and Metformin XR were almost identical between the FDC and reference products, demonstrating consistent drug release and absorption. No significant differences were observed in Tmax, t1/2, or other pharmacokinetic parameters, further supporting bioequivalence. Additionally, the FDC was well-tolerated, with no serious adverse events reported, and all subjects completed the study without complications.

Conclusion: The study confirmed that the FDC of Dapagliflozin, Sitagliptin, and Metformin XR is bioequivalent to the reference products in healthy adult males under fed conditions. This bioequivalence supports the use of the FDC as an effective treatment option to improve glycemic control in adults with T2D, particularly in the Indian context, promoting the benefits of combined therapy in managing diabetes.

Keywords: Bioequivalence, Fixed-dose combination (FDC), Type 2 diabetes (T2D), Pharmacokinetics, Dapagliflozin, Metformin XR, Sitagliptin

INTRODUCTION

Glycemic management in individuals with type 2 diabetes prevents complications and maintains quality of life.[1] According to current diabetic guidelines, lifestyle modification is recommended as well as the use of metformin as the first-line treatment for type 2 diabetes.[2] Metformin works primarily by improving insulin sensitivity in peripheral tissues and inhibiting hepatic gluconeogenesis.[3] Most patients with type 2 diabetes require additional treatment with add-on therapy to achieve additional glycemic control as their condition progresses over time.[4] Sodium-glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, thiazolidinedione, sulfonylureas, and basal insulin are the second-line drug alternatives added to metformin monotherapy.[2,5]

Dapagliflozin, an SGLT2 inhibitor, lowers blood glucose by inhibiting SGLT2 from reabsorbing glucose in the renal proximal tubule, leading to glycosuria and decreasing plasma glucose levels.[6,7] This drug improves glycemic control independent of insulin, with a low risk of hypoglycemia.[7,8] Dapagliflozin has other beneficial effects, which include body weight loss, natriuresis, and blood pressure reduction.

Metformin and Dapagliflozin have complementary mechanisms of action and may benefit patients with type 2 diabetes, with a low risk of hypoglycemia.[9] Because there is no pharmacokinetic (PK) interaction between Dapagliflozin and Metformin and the combination is well tolerated, Dapagliflozin can be safely co-administered with Metformin without a dose adjustment of either medication[10]. In two randomized, double-blind, three-arm 24-week trials comparing Dapagliflozin plus Metformin, Dapagliflozin alone, and Metformin alone in

treatment-naive individuals, a combination therapy significantly decreased the levels of HbA1c compared to either monotherapy.[11] Adding Dapagliflozin to the treatment regimen of patients with type 2 diabetes whose condition was poorly controlled by Metformin alone significantly improved glycemic control, according to the findings of a randomized, double-blind, placebo-controlled study.[12] Compared to Dapagliflozin or Metformin monotherapy, Dapagliflozin and Metformin combination therapy showed more significant improvements in any of the components of the metabolic syndrome.[13]

The current study provides evidence for considering triple FDC of Dapagliflozin plus Sitagliptin plus Metformin ER as an alternative option with minimal risk of hypoglycemia and weight gain while considering oral triple-combination therapy for patients to achieve their glycemic target.

METHODS

Study Subjects

Participants included in the study were healthy male volunteers over the age of 18 to 45 years with a body mass index of 18.50–30.0 kg/m^2 at the time of screening. The following were key exclusion criteria: a history of hypersensitivity to Dapagliflozin, Metformin, and Sitagliptin, or any excipient of the study drugs; clinically significant medical disorders; abnormal laboratory findings; difficulty in blood transfusion or blood donation within 90 days of first dosing of the study drug, Habit of consuming high caffeine (more than 5 cups of coffee or tea/day), smokers who smoke >9 cigarettes per day, alcoholics who consume >21 units of alcohol in a week, asthma, urticaria or other allergic reactions, dehydration from diarrhoea, vomiting, or any other reason within a period of 24.00 hours prior to study check-in, abnormal vitals, difficulty swallowing the investigational product. 2 subjects were withdrawn from the study due to adverse events, and the adverse event was resolved without any sequale.

Study Design and Blood Sampling Timepoints

An open label, randomized, balanced, two sequence, two period, cross-over, single-dose oral relative bioavailability study in healthy adult human male subjects under fed conditions. During each session, subjects were housed in the clinical facility from at least 11:00 hours before dosing until 24.00 hours after the dose. After each dosage, subjects were brought back to the clinical facility for ambulatory samples at 48.00 and 72.00 hours. In each period, subjects were provided with a standard meal; appropriate drinking water and posture restrictions were ensured after dosing in the study, as well as all the subjects were continuously monitored for their well-being and safety throughout the study. All the restrictions and prohibitions for diet and drinking water, posture, and housing areas as specified in the protocol were followed and complied with by all the subjects in the study.

A clinical study was conducted over 12 days. A washout of 07 days was maintained between each consecutive dosing period.

The descriptive statistics for the pharmacokinetic parameters are the area under the plasma concentration-time curve from time 0 to the last quantifiable data point (AUC_{0-t}) for Dapagliflozin and Metformin; the area under the plasma concentration-time curve from time 0 to 72 hours (AUC_{0-72}) for Sitagliptin; and the peak plasma concentration (C_{max}) for Dapagliflozin, Sitagliptin, and Metformin. Each endpoint was log-transformed before fitting the model. Log treatment differences estimated from that model were afterward back-transformed to the original scale to obtain the geometric mean ratio of FDC to reference products. Bioequivalence would be met if the adjusted geometric mean ratios (FDC to free combination) and two-sided 90% confidence intervals (CIs) of AUC and C_{max} for each component were within 80.00–125.00%. Secondary endpoints were to monitor the adverse events and to ensure the safety of the subjects following administration of a single dose of Dapagliflozin 10mg, Sitagliptin 100mg, and Metformin 1000mg extended-release tablets.

The Independent Ethics Committee gave their approval to the study protocol. The Declaration of Helsinki's ethical principles and Good Clinical Practice guidelines were followed in conducting this study at Notrox Research Pvt Ltd, Bangalore, Karnataka.[14] Each subject received written and oral information about the study before participation, and they provided their written informed consent.

This study consisted of the crossover designs, and there was a 7-day washout period between the two treatment periods. During each study period, the subjects received a single oral dose of the test formulation Dapagliflozin 10 mg plus Sitagliptin 100 mg plus Metformin 1000 mg Extended Release Tablets (T) Manufactured by Exemed Pharmaceuticals, Gujarat, India, or Januvia® Sitagliptin 100mg Tablets (R1) Manufactured by MSD Pharmaceuticals Pvt. Ltd., at M/s. Recipharm Pharmaservices Pvt. Ltd., Bangalore, and Xigduo® XR Dapagliflozin 10 mg plus Metformin 1000 mg Extended Release Tablets (R2) Manufactured by AstraZeneca Pharmaceuticals LP, 4601 Highway, 62 East Mount Vernon, Indiana 47620, USA.

Before receiving the study drug, subjects were admitted to the Clinical Trial Centre of Notrox Research Pvt. Ltd., Bangalore, Karnataka. The subjects were administered the study medication in the fed state. The study drug was given to participants who had previously consumed a high-calorie and fat breakfast with 240±2 mL of 20% aqueous glucose solution followed by 60 mL of the glucose solution administered every 15 minutes (window period of ± 5 minutes) for up to 4 hours after dosing at ambient temperature under fed conditions.

The subjects who completed the PK sampling for 24 hours were discharged on day 2, and an additional visit for the last PK sampling was made on days 3 and days 4.

Blood samples were collected up to 72 hours after dosing (at 0, 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00,

3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 10.00, 12.00, 16.00, 24.00, 48.00, and 72 hours). Following centrifugation (3,500 rpm) for 10 minutes at 2-5°C, the plasma was transferred to two polypropylene tubes and frozen at -70 ± 10°C before analysis.

Measurement of plasma Dapagliflozin, Metformin and Sitagliptin

Dapagliflozin, Metformin and Sitagliptin plasma concentrations were measured by Notrox Research Pvt Ltd., Bangalore, Karnataka, using validated ultra-performance liquid chromatography (UPLC) methods in conjunction with mass spectrometry (MS/MS).[15]

PK and statistical analysis

Statistical analysis was carried out using the SAS® statistical software, version 9.4 of SAS Institute Inc., USA. The pharmacokinetic analysis was performed on subjects who completed both periods of the study. The descriptive statistics (mean, median, minimum, maximum, standard deviation, and coefficient of variation) for the pharmacokinetic parameters (primary parameters: C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ and secondary parameters: t_{max}, $t_{1/2}$, K_{el}, and $AUC_{\_\%Extrap\_obs}$) were estimated for both test and reference products. The Ln-transformed pharmacokinetic parameters (AUC_{0-t} and $AUC_{0-\infty}$) were analyzed using an ANOVA model. The analysis of the variance model included sequence, treatment, period, and subject as a fixed effect. To test the two one-sided tests for bioequivalence, ratio analysis and 90% confidence intervals for the difference between the treatment's least-square mean were calculated for Ln Transformed AUC_{0-t}, and $AUC_{0-\infty}$. The confidence interval is expressed as a percentage difference relative to the LSM of the reference treatment.

The 90% confidence intervals for Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} are within the bioequivalence limits of 80.00 to 125.00%.

Safety assessments

Safety measurements of blood pressure, pulse rate, and body temperature were performed as specified in the study protocol, and subjects' well-being questionnaires were also performed at all the scheduled times of vitals recording. Monitoring for adverse events was conducted at the time of recording of subject well-being as well as throughout the entire study duration. There were no serious adverse events reported in the study. Based on the review of the clinical and laboratory safety data, the safety profile of both the investigational products (test and reference) was found to be safe after exposing the healthy volunteers.

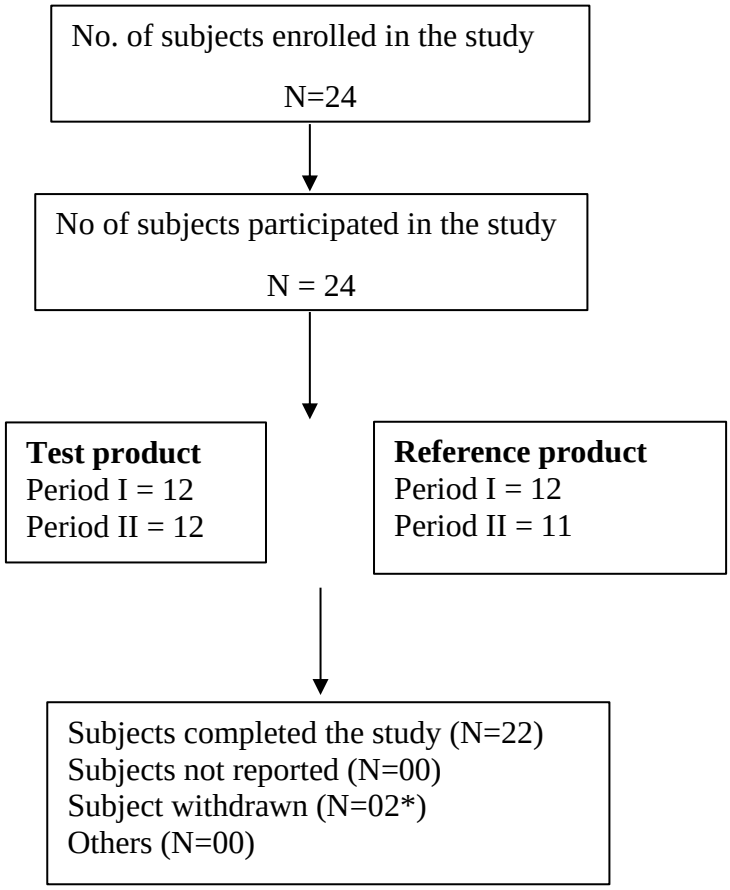

Figure 1: Flow diagram of the study

RESULTS

Demographic data

Out of the 24 participants that were recruited in the study, 22 of them completed it. Table 1 provides a summary of the research population's demographic data.

Pharmacokinetic parameters

Based on data obtained from subjects who completed the test and reference products, the following pharmacokinetic parameters were calculated.

Table 1: Summarized Demographic Profile of Subjects

Parameter	Mean	SD	Minimum	Maximum	CV%
Age (Years)	31.86	6.21	19.00	43.00	19.47
Height (H)	1.69	0.06	1.55	1.77	3.29
Weight (KG)	72.16	11.59	55.10	90.00	16.06
BMI (Kg/m^2)	25.18	3.29	19.52	29.48	13.08

Table 2: Statistical Results of Log Transformed Test product (T) versus Reference product (R) Dapagliflozin

Pharmacokinetic Parameter	Geometric Least Square Mean		ISCV (%)	T/R Ratio (%)	Power (%)	90% Confidence Test Interval
	Test Product (T)	Reference Product (R)				
C_{max} (ng/mL)	132.7381	123.9223	30.23	102.96	69.18	88.23 TO 120.15
AUC_{0-t} (ng.hr/mL)	883.5399	840.2715	13.84	105.15	99.70	97.85 TO 112.99
$AUC_{0-\infty}$ (ng.hr/mL)	988.9141	930.1807	17.56	106.31	97.39	97.06 TO 116.45

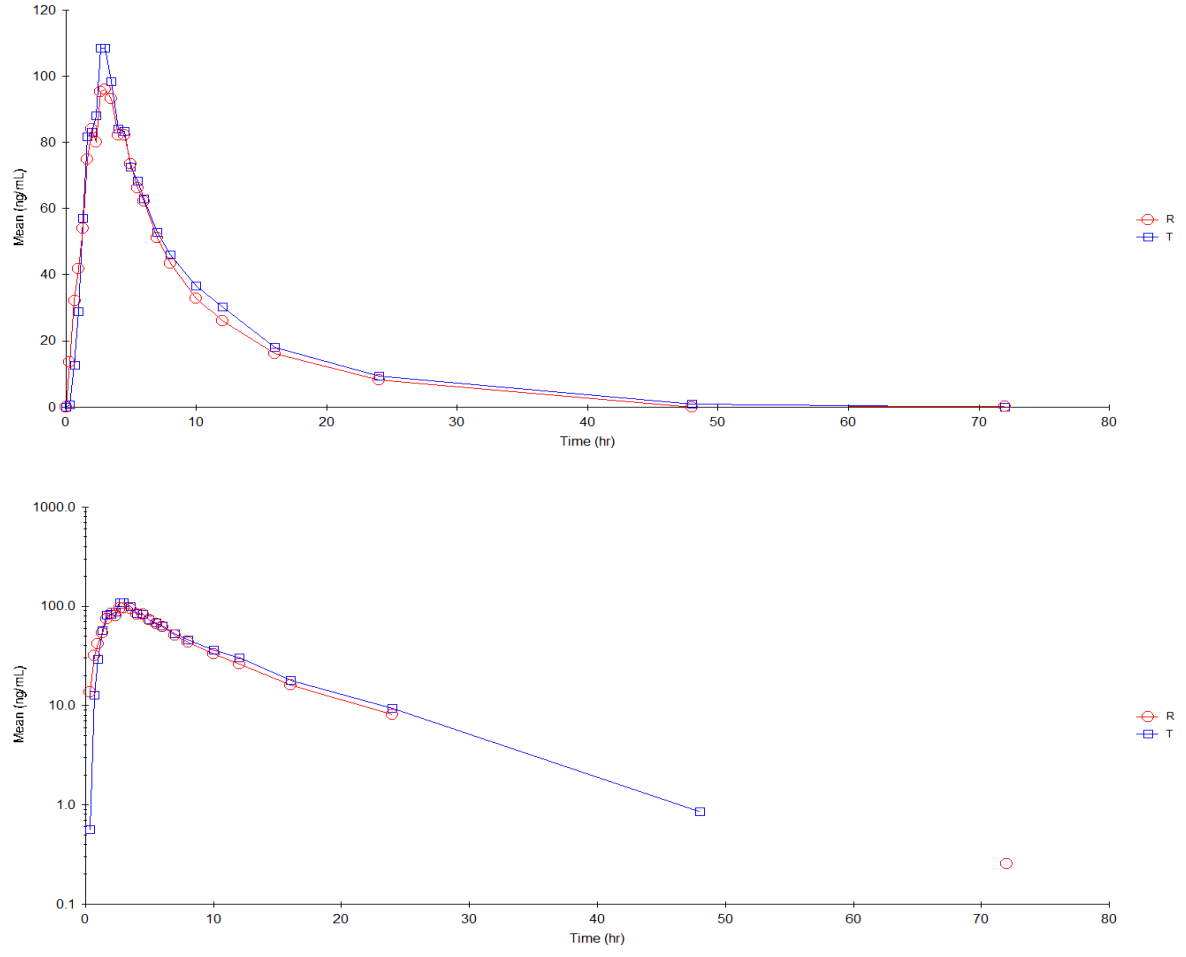

Figure 2: Mean plasma concentration-time curve of Dapagliflozin following a single oral administration of Dapagliflozin 10 mg + Sitagliptin 100 mg + Metformin 1000 mg Extended Release Tablets (T) vs. Dapagliflozin 10 mg + Metformin 1000 mg Extended Release Tablets (R) in 24 healthy subjects.

Table 3: Statistical Results of Log Transformed Test product (T) versus Reference product (R) Sitagliptin

Pharmacokinetic Parameter	Geometric Least Square Mean		ISCV (%)	T/R Ratio (%)	Power (%)	90% Confidence Test Interval
	Test Product (T)	Reference Product (R)				
C_{max} (ng/mL)	361.7459	347.6147	19.29	104.07	95.06	94.18 TO 114.99
AUC_{0-t} (ng.hr/mL)	4564.1249	4549.5024	21.04	100.32	91.86	89.99 TO 111.84
$AUC_{0-\infty}$ (ng.hr/mL)	4932.8070	4925.4935	20.89	100.15	92.17	89.9 TO 111.56

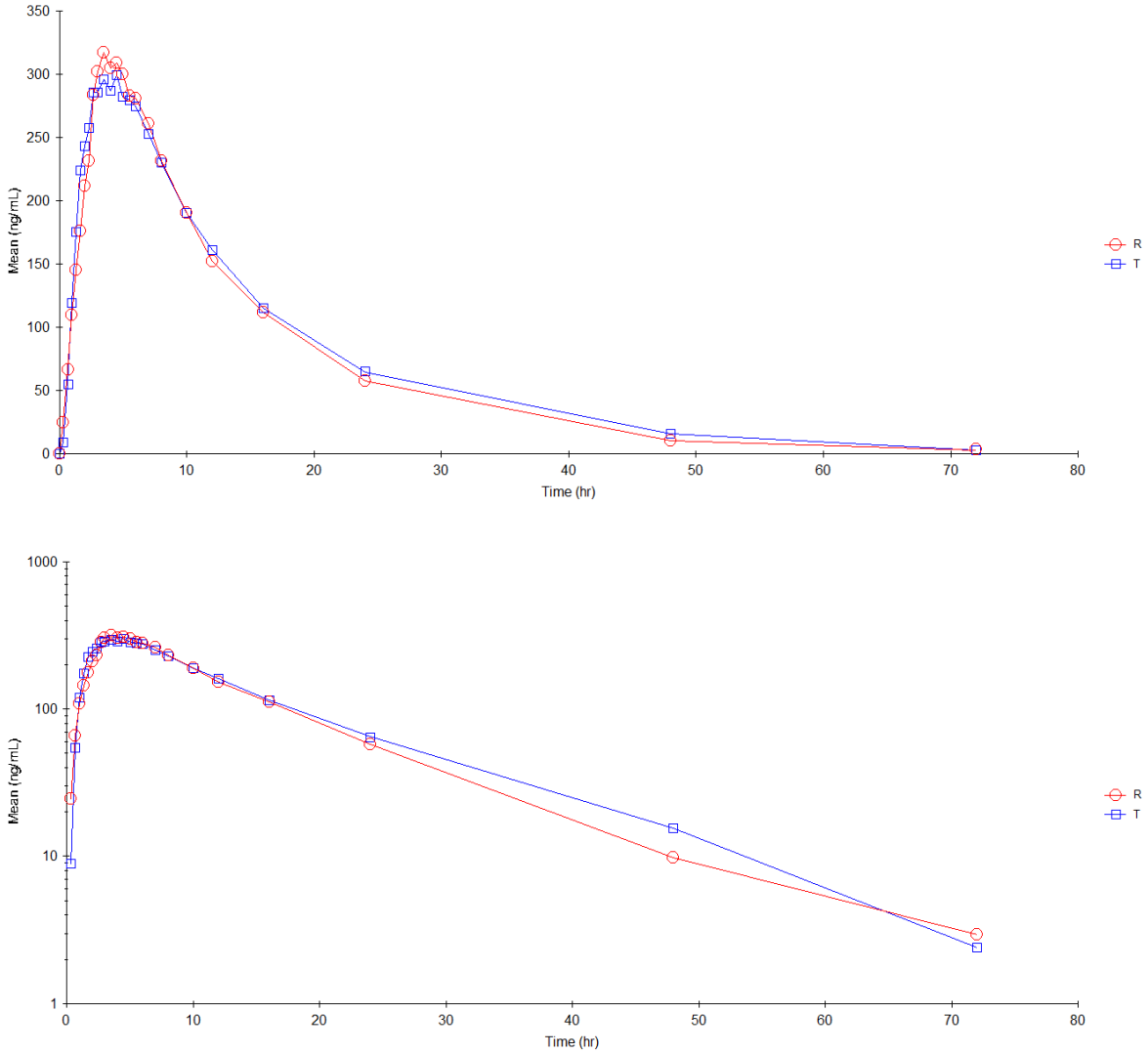

Figure 3: Mean plasma concentration-time curve of Sitagliptin following a single oral administration of Dapagliflozin 10 mg + Sitagliptin 100 mg + Metformin 1000 mg Extended Release Tablets (T) vs. Sitagliptin 100 mg Tablets (R) in 24 healthy subjects.

Table 4: Statistical Results of Log Transformed Test product (T) versus Reference product (R) Metformin

Pharmacokinetic Parameter	Geometric Least Square Mean		ISCV (%)	T/R Ratio (%)	Power (%)	90% Confidence Test Interval
	Test Product (T)	Reference Product (R)				
C_{max} (ng/mL)	1324.7251	1418.9534	19.44	93.36	94.81	84.43 TO 103.24
AUC_{0-t} (ng.hr/mL)	18803.894	18734.876	25.36	100.37	81.60	88.1 TO 114.35
$AUC_{0-\infty}$ (ng.hr/mL)	20060.614	19736.035	24.71	101.64	83.27	89.51 TO 115.42

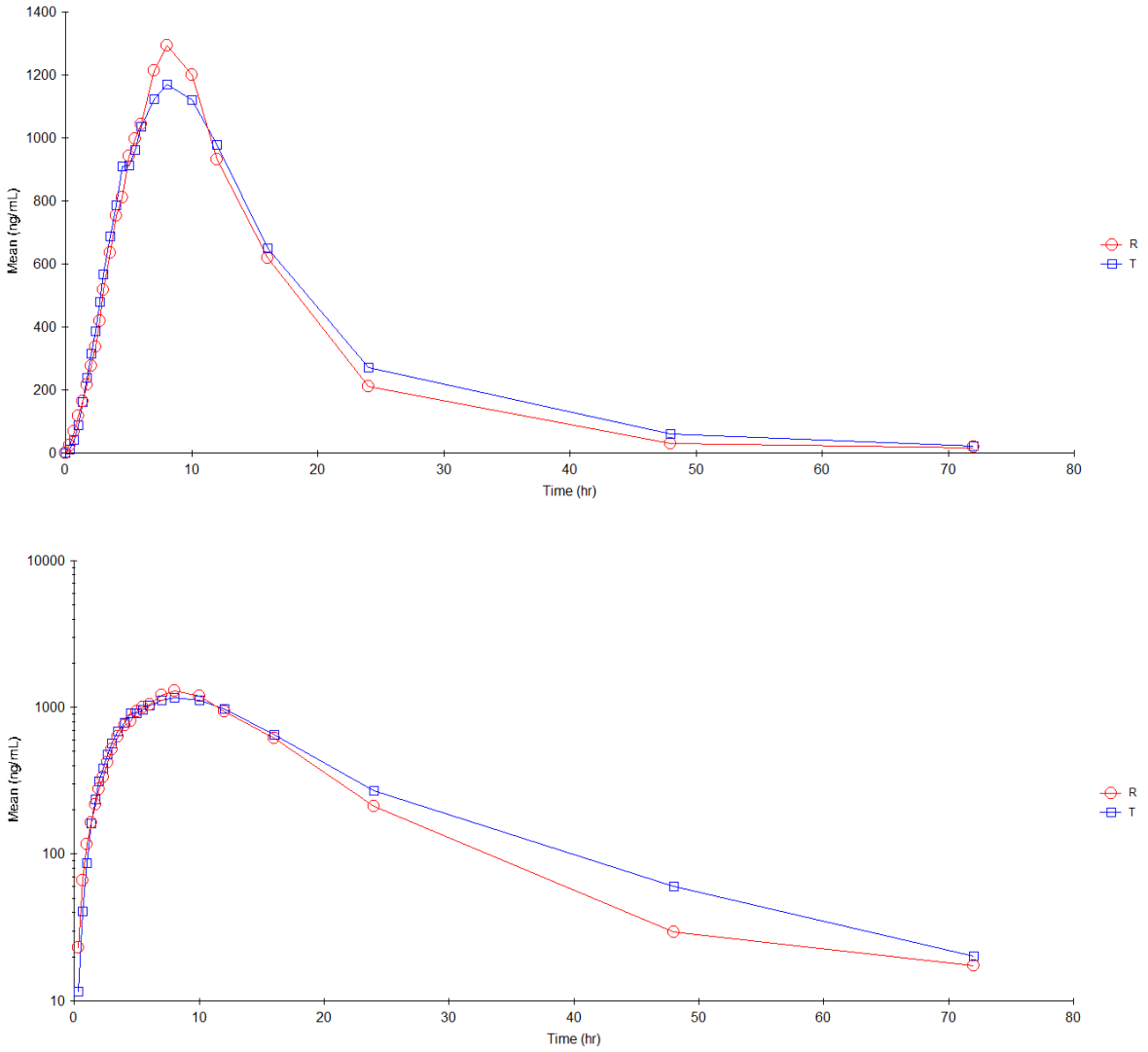

Figure 4: Mean plasma concentration-time curve of Metformin following a single oral administration of Dapagliflozin 10 mg + Sitagliptin 100 mg + Metformin 1000 mg Extended Release Tablets (T) vs. Dapagliflozin 10 mg + Metformin 1000 mg Extended Release Tablets (R) in 24 healthy subjects.

Safety and tolerability assessments

The adverse event was found to be mild in severity and possibly related to the medicine being studied. The adverse event was settled with no aftereffects and the participant in the study was withdrawn. In the fed study, The AE rates of the two formulations did not differ significantly. The study's recorded adverse events (AEs) cleared on their own without the need for special care. Neither the reference formulation nor the test formulation provoked any major or severe adverse events (AEs) throughout study.

DISCUSSION

FDC formulation of extended-release tablets comprising dapagliflozin (10 mg), sitagliptin (100 mg), and metformin (10 mg), formulated by Exemed Pharmaceuticals, Gujarat, India. Reference product 2 is utilized as Januvia®, which includes Sitagliptin 100 mg Tablets, and Reference product 1 is used as Xigduo® XR, which comprises Dapagliflozin and Metformin HCl XR (10 mg/1,000 mg). The PK parameters as well as safety assessments of the test formulations and the formulation used as a reference were contrasted in healthy individuals in this open-label, randomized, two-period crossover trial. Bioequivalence of the two formulations was determined in this study while the subjects were fed settings.

In fed states, the single-dose administration of Januvia® Sitagliptin 100 mg Tablets, Xigduo® XR Dapagliflozin 10 mg plus Metformin 1000 mg Extended-Release Tablets, and Dapagliflozin 10 mg in addition to Sitagliptin 100 mg plus Metformin 1000 mg Extended-Release Tablets proved to be safe and well-tolerated. No serious or major side effects were observed throughout the study. This result validates the development and application of the novel FDC tablet as a substitute formulation for the brands' Sitagliptin 100 mg Tablets and Dapagliflozin 10 mg plus Metformin 1000 mg Extended-Release Tablets. The study included the enrollment of 24 adult male individuals of good health. Out of the 24 participants that were enrolled, 24 of them took part in the study, while 22 of them completed both phases. The study carried out on

subjects 006 and 007 was discontinued. At the stage of check-in during Period II, Subject 007 was discontinued. Over the course of 12 days, the clinical study was carried out. Between every subsequent dose interval, a washout of seven days was established. The subject safety assessment results obtained from the conduct of this study lead us to conclude that the overall condition of health of participating subjects was confirmed to be clinically suitable. And also, both the investigational products have been found to be both safe and well-tolerated in the individuals at the chosen dosage range. The 90% confidence intervals for Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} are within the bioequivalence limits of 80.00 to 125.00%.

Following the completion of the study's clinical phase and evaluation of the vital sign measures, The findings of the post-study laboratory tests and the general health status of all subjects were determined to be clinically fit. Both used products in this study were well tolerated in subjects who took part in study.

CONCLUSION

Ultimately, our findings revealed that the two assessed dosages of the Dapagliflozin/Sitagliptin/Metformin XR FDC tablets exhibited bioequivalency with their corresponding reference products. The FDC's safety profiles were equivalent to the established safety profiles of the individual drugs, and it was tolerated well. Based on the data obtained so far, it appears that the triple FDC medication may offer an alternate course of therapy to the conventional stepwise treatment strategy for managing type 2 diabetes. In addition, for patients with type 2 diabetes who need numerous glucose-lowering medications, this triple FDC may assist to enhance adherence and achieve glycemic objectives as well as outcomes.

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Competing interests/Conflicts of interest: Dr. Rajashree Dhar, Dr. Ashish Prasad, and Dr. Vivekanandan Annadurai are the employees of USV Pvt. Ltd.

Informed Consent: Informed Consent is applicable

Ethical approval: The study was approved by the Independent Ethics Committee

Author Contributions: Dr. Rajashree Dhar, Dr. Ashish Prasad, Dr. Vivekanandan Annadurai. All authors have worked together on project development, literature research, manuscript writing, and editing.

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