Future Journal of Pharmaceutical Sciences

RESEARCH Open Access

Bioequivalence study of different brands of vildagliptin in healthy human subjects

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Abstract

Background: Vildagliptin is a dipeptidyl peptidase-4 inhibitor used to treat diabetes mellitus. No bioequivalence study data have been published for the Indian population comparing bioequivalence of vildagliptin brands Galvus, Zomelis, and Jalra. This study aimed to evaluate the bioequivalence between three brands of vildagliptin 50 mg tablet (test 1, Zomelis; test 2, Jalra; and reference, Galvus) and to compare these test formulations with the reference formulation to meet the regulatory requirements of bioequivalence of CDSCO, India. The study was conducted in the clinical research center of the college after enrolling 12 healthy volunteers. This study was a single-dose, randomized, open-label, balanced, three treatment, three period, under fasting condition in 12 adult healthy volunteers. After overnight fasting, the subjects received a single dose of either of any three brands of the vildagliptin tablet (T1—test 1; T2—test 2; and R—reference). The washout period was 7 days. Randomization was in the way of T1T2R in the first period, T2T1R in the second period, and RT1T2 in the third period. Blood samples were collected, after that drug concentration in the plasma was measured with the help of HPLC. Outcome measures 90% confidence interval of the geometric mean ratios (test/reference) for the LnC_{max}, LnAUC0-t, and LnAUC0-∞ was calculated.

Results: The AUC0-t was 1390.03, 1401.50, and 1409.37 ng h/ml for the T1, T2, and R, respectively. C_{max} was 287.89, 287.41, and 285.17 ng/ml for the T1, T2, and R, respectively. AUC0-∞ was 1452.03, 1467.59, and 1473.53 ng h/ml for the T1, T2, and R, respectively. No significant difference was observed in the pharmacokinetic parameters between the T1, T2, and R. The geometric mean ratios for T1/R for LnC_{max}, LnAUC0-t, and LnAUC0-∞ were 1.0014 (90% CI, 1.0002–1.0026), 0.9992 (90% CI, 0.9971–1.0013), and 0.9994 (90% CI, 0.9973–1.0016), respectively. For the T2/R, geometric mean ratios for LnC_{max}, LnAUC0-t, and LnAUC0-∞ were 1.0003 (90% CI, 0.9992–1.0013), 0.9988 (90% CI, 0.9969–1.0008), and 0.9985 (90% CI, 0.9961–1.0010), respectively.

Conclusion: In this single-dose study involving Indian healthy volunteers under fasting conditions, the three brands of vildagliptin (Zomelis, Jalra, and Galvus) were bioequivalent as per the bioequivalence criterion of CDSCO, India.

Keywords: Vildagliptin, Indian population, Schedule Y, Bioequivalence, CDSCO

Background

Diabetes mellitus is a metabolic disorder which is characterized by hyperglycemia with disturbances in the metabolism of carbohydrates, fats, and proteins which results because of the defects in secretion of insulin, action of insulin, or both. Thirst, polyuria, blurring of vision, and weight loss are the characteristic symptoms of diabetes [1]. Gliptins are prominent medications in type 2 diabetes management as five different molecules have commercialized, and they are also in combination with metformin [2]. Vildagliptin is one of gliptin drugs. Dipeptidyl peptidase 4 (DPP-4, DPP-IV) is found in the plasma, kidney, and brush-border membranes of the intestine, hepatocytes, on capillary endothelial cells' surface, and a subset of T lymphocytes [3]. DPP-4 rapidly inactivate incretin glucagon-like peptide 1 (GLP-1) and

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glucose-dependent insulinotropic peptide. GLP-1 stimulates postprandial-induced insulin secretion and leads to glucose homeostasis [4, 5]. GLP-1, which is in circulation, degraded rapidly, and its degradation is inhibited by DPP-4 [3, 6]. Inhibition of DPP-4 enzyme activity leads to GLP-1-increased activity; hence glycemic, control increased in human trials [7–9]. Therefore, augmentation of this GLP-1 activity in diabetic patients leads to lowering of glycemia [4, 10, 11]. Vildagliptin (1-[[3-hydroxy-1-adamantyl) amino] acetyl]-2-cyano-(S)-pyrrolidine) is orally active and highly selective inhibitor of DPP-4 [12]. After oral administration of vildagliptin, it is speedily absorbed, and it has eighty-fifth absolute bioavailability. Vildagliptin have low protein binding (9.3%); it equally distributes between the plasma and red blood cells. Eighty-five percent of the oral dose is ultimately excreted by the kidney as either metabolites or unchanged vildagliptin [13, 14]. Vildagliptin is a proprietary drug of Novartis, and it is sold under the brand name *Galvus*. Novartis licensed the drug to Abbott, USV, and Emcure [15]. Abbott sells vildagliptin as Zomelis, USV sells it as Jalra, and Emcure sells it as Vysov. These brands of vildagliptin recorded the sale of 822 crore out of 10,000 crore market of antidiabetic drugs in the year 2016 [16]. In our study, we decided to take three brands of vildagliptin Zomelis, Jalra, and Galvus to check their bioequivalence. Here, Zomelis was taken as test 1 drug (T1), Jalra was taken as test 2 (T2) drug, and Galvus was taken as the reference drug (R). The prices of these formulations are nearly the same.

Methods

Aim of the study

This study was done to evaluate the bioequivalence of three different brands of vildagliptin tablet (50 mg) formulations following single-dose administration in healthy volunteers after an overnight fasting of 10 h in order to compare the bioequivalence of these preparations.

Compliance with ethical standards

For the compounds to be bioequivalent, the compounds should have the calculated 90% confidence interval for AUC and C_{max} within the bioequivalent range, usually 80–125% [17]. Informed consent was taken from all the subjects as per the specifications of the Central Drug Standard Control Organization. The Institutional Review Board of our university approved this study protocol and informed consent. This study was conducted as per the Declaration of Helsinki and Good Clinical Practices as per the schedule Y of Drug and Cosmetic Rule 1945 of India and Central Drug Standard Control Organization (CDSCO) [18, 19]. This study was not funded by any organization, and no conflict of interest was reported.

Subjects

Twelve healthy Indian male volunteers between the age group of 18 and 25 years were enrolled in the study, and their body mass index was in the range of 18.50–24.90 kg/m^2 (both inclusive) [20]. Written informed consent was taken from all volunteers before the start of the study. For the subjects, some exclusion criteria were there.

Study design and procedures

This study was single-dose, open-label, randomized, 3-treatment, 3-period. After a night fasting, the subjects took a single dose of either of any three brands of the vildagliptin tablet {T1 (Batch No. BF488), T2 (Batch no. BE448), R (Batch no.BL218)}. There were 7 days of washout period between each period of the study. The randomization schedule was like T1T2R in the first period, T2T1R in the second period, and RT1T2 in the third period (T1 = Zomelis, T2 = Jalra, and R = Galvus). The study was explained to each subject, and a written informed consent was taken from each subject according to the Schedule Y of the Drug and Cosmetic Act and Rules 1945 of India. After taking the informed consent, a clinical examination was done for the subjects. Routine clinical tests were performed at the DIPSAR Clinical Research Laboratory 1 week before the start of the study. Before the dose administration, the subjects were enrolled in the clinical research center of DIPSAR and were kept confined to the center for the duration of the study. A peripheral venous catheter was placed in the antecubital vein of the subjects, and it was flushed with 0.5 ml of heparin in normal saline (NS) solution (1:20). To get samples free from NS solution and heparin, first, 1 ml of blood was discarded. For the determination of the amount of vildagliptin in the plasma, blood samples (4 ml) were collected in K2EDTA vacutainers at the following given times: predose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 h. These blood samples were centrifuged at 2500 rpm for 15 min at 4 °C. The resulting plasma samples were separated and stored at − 75 °C until analysis. For the adverse events, subjects were monitored for 24 h during the study using clinical measurements like blood pressure (BP), pulse rate, and body temperature and by orally asking any complaint felt by the subjects.

Determination of vildagliptin plasma concentration

Plasma concentrations of vildagliptin were determined in the Clinical Research Center Laboratory of DIPSAR, using a validated HPLC-UV method. HPLC system used was of Shimadzu Corporation (LC-2010C HT) model. The HPLC components consist of the following equipment: System Controller (LC-2010HT), Sample Cooler (LC-2010CHT), Degasser (5 line degasser), Column

Oven, Autosampler injector, Pump (4 pump system), UV-visual detector, and reservoir tray. Vildagliptin was extracted from the plasma by using the protein precipitation extraction method. Plasma samples which were stored at − 75 °C were taken out from the deep freezer. The method which was followed was a slightly modified version of Santhakumari et al.'s method [20]. An aliquot of 210 μl plasma was taken into the Eppendorf tubes and added 50 μl of internal standard dilution (tolbutamide 1000 ng/ml) and then it was vortexed to mix the contents; 1200 μl methanol was used as a precipitating solvent to precipitate vildagliptin. After that, it was vortexed for 1 min, and after that, it was centrifuged at 4 °C, 7000 rpm for 10 min. The resulting supernatant was taken out and transferred to HPLC vials. The mobile phases which were used in this method were 50 mM ammonium bicarbonate (pH 7.8) (phase A) and 100% acetonitrile (phase B). One milliliter per minute was the flow rate of mobile phases. The chromatographic system consisted of a C-18 column, and the UV detector was set at 210 nm (Table 1). The total run time was 20 min. The injection volume was 20 μl.

Statistical methods and data analysis

Pharmacokinetic analysis

There was no dropout of subjects in the study, and all the subjects participated till the last period of the study. To determine the pharmacokinetic parameters of vildagliptin, the non-compartmental pharmacokinetic method was employed. By visual inspection of each subject's plasma, concentration-time profile maximum plasma concentration (C_{max}, ng/ml) and time to reach peak plasma concentration (T_{max}, h) were obtained. The area under the curve (AUC) from time 0 to the last measurable concentration time ($AUC_{0\text{-}t}$) was calculated by the trapezoidal method. Microsoft Excel was used as the software to calculate various parameters in this bioequivalence study. The $t_{½}$ (h) was calculated as $0.693/k_{el}$ where k_{el} is terminal elimination rate constant. The AUC from time 0 to infinite time ($AUC_{0\text{-}\infty}$) was calculated as $AUC_{0\text{-}t} + C_t/k_{el}$; here, C_t represents the last quantifiable concentration, and k_{el} represents the terminal elimination rate constant. k_{el} was calculated by least-squares regression analysis during the terminal log-linear phase of the concentration-time curve [21, 22].

Statistical analysis

To determine the bioequivalence between the products, analysis of variance (ANOVA) at $\alpha = 0.05$ was performed to determine the statistical differences of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ which represented the rate and extent of drug absorption. ANOVA was performed on the logarithmically (Ln) transformed data of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$. The bioequivalence between the three formulations was assessed by calculation of the 90% confidence interval for the ratios of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ obtained after the administration of the three formulations using logarithmically transformed data. For the products to be bioequivalent, the requirement is the 90% CI of the C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ to be within the acceptance criteria of 0.8–1.25 (CDSCO guidelines, 2005). Any statistical difference at $P < 0.05$ was considered as significant.

Results

Bioanalytical method

The calibration curve of vildagliptin was linear ranging from 10 to 1000 ng/ml, and the linear regression of the drug concentration versus peak height ratios (vildagliptin/IS) gave coefficients of determination (r^2) = 0.9992. The lower limit of quantitation was 10.0 ng/ml with the accuracy (%) and precision (CV %) of 97.37and 1.48, respectively.

Inter-formulation variations between T1/T2 and R were analyzed by significance testing (ANOVA) for each logarithmically transformed data of $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$,

Table 1 Optimized chromatographic conditions for the analysis of vildagliptin by RP-HPLC

Drug	Time (min)	Mobile buffer (%A)	Phase ACN (%B)	Flow rate (ml/min)	Detection wavelength (nm)	Injection volume (μl)	Retention time (min)
Vildagliptin	0	95	5				
	5	80	20				
	10	50	50				
	15	20	80	1	210	20	11
	17	5	95				
	19	95	5				
	20	95	5				

Linear regression was performed to determine the drug concentration in the range of 10–1000 ng/ml (r^2 = 0.9992). The lower limit of quantitation was 10.0 ng/ml with the accuracy (%) and precision (CV %) of 97.37 and 1.48, respectively

and C_{max}, with the results of F values and P values were as given below:

ANOVA of C_{max}

Source of variation	*SS*	*df*	*MS*	*F*	*P value*	*F crit*
Rows	0.000894	11	8.13E−05	4.628591	0.001101	2.258518
Columns	0.000118	2	5.92E−05	3.374427	0.052702	3.443357
Error	0.000386	22	1.76E−05			
Total	0.001399	35				

ANOVA of AUC_{0-t}

Source of variation	*SS*	*df*	*MS*	*F*	*P value*	*F crit*
Rows	0.000723	11	6.57E−05	0.767611	0.667168	2.258518
Columns	0.000216	2	0.000108	1.261262	0.302993	3.443357
Error	0.001883	22	8.56E−05			
Total	0.002822	35				

ANOVA of $AUC_{0-\infty}$

Source of variation	*SS*	*df*	*MS*	*F*	*P value*	*F crit*
Rows	0.001064	11	9.67E−05	0.859377	0.588844	2.258518
Columns	0.000257	2	0.000128	1.141905	0.337415	3.443357
Error	0.002475	22	0.000113			
Total	0.003796	35				

Bioanalytical method *(Continued)*

Pharmacokinetic analysis

The mean plasma concentration vs. the time profile of all the three formulations in the 12 treated healthy subjects is shown in Fig. 1. After oral administration, the drug was absorbed rapidly of all three formulations, and it was available to the systemic circulation. Peak plasma concentrations (averaged) were 287.89, 287.41, and 285.17 ng/ml after the oral administration of the test 1, test 2, and reference formulations, respectively. The concentrations were reached at a mean time of 1.8 h after drug administration for all three formulations. The AUC_{0-t} and $AUC_{0-\infty}$ values averaged 1390.03 and 1452.03 after the administration of the test 1 formulation, 1401.50 and 1467.59 ng h/ml after the administration of test 2 formulation, and 1409.37 and 1473.35 ng h/ml after the administration of the reference formulation, respectively. The data are shown in Table 2.

Bioequivalence analysis

The mean ratio and the 90% confidence interval for Ln-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ are presented in Table 3. The lower and upper limits of the

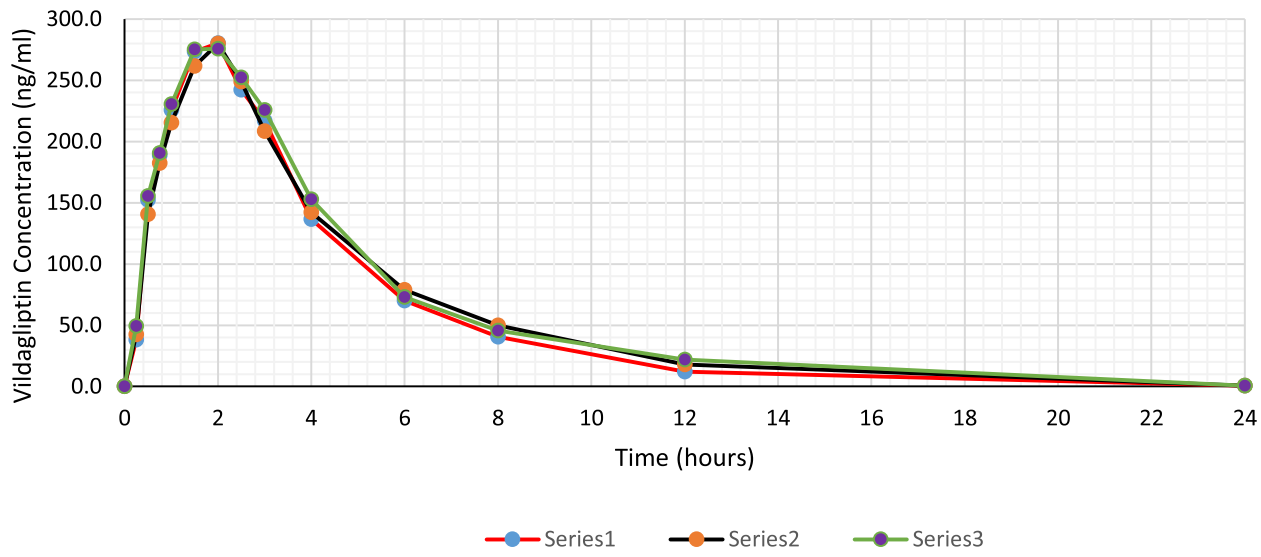

Fig. 1 Mean plasma concentrations of vildagliptin after the administration of test 1, test 2, and reference formulations. Here, series 1 = test 1, series 2 = test 2, and series 3 = reference

Table 2 Mean vildagliptin pharmacokinetic parameters (± SD) after the last administration of the test 1, test 2, and reference formulations

Parameter	Test 1 formulation	Test 2 formulation	Reference formulation
C_{max} (ng/ml)	287.89 ± 3.51	287.41 ± 3.63	285.17 ± 5.01
T_{max} (h)	1.79 ± 0.26	1.79 ± 0.25	1.79 ± 0.27
$AUC_{0\text{-}t}$ (ng h/ml)	1390.03 ± 23.81	1401.50 ± 30.70	1409.37 ± 30.29
$AUC_{0\text{-}\infty}$ (ng h/ml)	1452.03 ± 32.97	1467.59 ± 38.06	1473.35 ± 32.97
$t_{½}$ (h)	2.59 ± 0.14	2.66 ± 0.16	2.63 ± 0.09
K_{el} (h^{-1})	0.2678 ± 0.0160	0.2605 ± 0.0156	0.2617 ± 0.0096

90% confidence intervals were 1.0002–1.0026 for LnC_{max}, 0.9971–1.0013 for Ln $AUC_{0\text{-}t}$, and 0.9973–1.0016 for $LnAUC_{0-\infty}$ of the test 1 formulation. The lower and upper limits of the 90% confidence intervals were 0.9992–1.0013 for LnC_{max}, 0.9969–1.0008 for $LnAUC_{0\text{-}t}$, and 0.9961–1.0010 for $LnAUC_{0-\infty}$ of the test 2 formulation. It can be seen that these values lie in the range of bioequivalence (0.80–1.25). The C_{max} values of vildagliptin after the administration of the three formulations did not differ significantly.

Discussion

Vildagliptin is a new orally effective antihyperglycaemic drug used in the treatment of type 2 diabetes. It is a specific inhibitor of dipeptidyl peptidase-IV (DPP-IV) inhibitor [23]. This inhibition prevents the degradation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). It leads to improve glycaemic control which is determined by glycated hemoglobin (HbA(1c)) and fasting plasma glucose (FPG) levels, and pancreatic alpha and beta cell functions also enhanced by the use of vildagliptin [24]. There were no adverse events encountered in this study. The objective of this study was to evaluate the bioequivalence of three brands of vildagliptin 50 mg tablet as test 1, test 2, and reference tablet which were administered as a single dose orally. As per the protocol, primary pharmacokinetic parameters $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} were evaluated. According to the protocol, any concentration lower than the lower limit of quantification was considered as 0. Extrapolated AUC of vildagliptin was low having a mean value of 4.5% after the administration of the test 1 formulation, 4.7% of the test 2 formulation, and 4.6% of the reference formulation. It was less than 20% of $AUC_{0\text{-}t}$ which indicates that the time used for checking the bioequivalence between the products was good enough to calculate the plasma concentration-time profile of the drug. The 90% confidence intervals were calculated for test 1/reference tablet and test 2/reference tablet of LnC_{max}, $LnAUC_{0\text{-}t}$, and $LnAUC_{0\text{-}\infty}$ of vildagliptin. After this, these confidence intervals were compared with the acceptance range of bioequivalence which is 0.80–1.25 as per the CDSCO criterion for bioequivalence [19]. In our study, we found that the 90% confidence interval of the test 1 and test 2 formulations of vildagliptin was within the bioequivalence criterion set for bioequivalence by CDSCO, India. For the C_{max} values, no statistical difference was observed after the oral administration of vildagliptin tablet formulations of the test 1, test 2, and reference formulations. Based on this study, it can be stated that these three formulations of vildagliptin test 1, test 2, and reference (Zomelis, Jalra, and Galvus) are bioequivalent. The findings of this study can be used in the future for the purpose of bioequivalence and pharmacokinetic profiling of the vildagliptin; however, further studies can be done on it by taking more numbers of healthy subjects, more

Table 3 90% confidence intervals of LnC_{max}, $LnAUC_{0-t}$, and $LnAUC_{0-\infty}$ from the test formulations to the reference formulation

Pharmacokinetic parameter	Geo mean ratio Test/reference		90% confidence interval (lower limit-upper limit)		
	T1/R	T2/R	Test 1	Test 2	Bioequivalence range
LnC_{max}	1.0014	1.0003	1.0002–1.0026	0.9992–1.0013	0.80–1.25
$LnAUC_{0-t}$	0.9992	0.9988	0.9971–1.0013	0.9969–1.0008	0.80–1.25
$LnAUC_{0-\infty}$	0.9994	0.9985	0.9973–1.0016	0.9961–1.0010	0.80–1.25

Bioequivalence interpretation requires the 90% confidence intervals to be within the acceptance criteria of 0.8–1.25

sensitive analytical methods, and more advanced software for the calculation of the pharmacokinetic profile.

Conclusion

In this single-dose study involving healthy male volunteers under fasting conditions, the three brands of vildagliptin ((1) Zomelis, (2) Jalra, and (3) Galvus) were found to be bioequivalent as per the bioequivalence criterion of CDSCO, India. Further studies can be done to compare vildagliptin bioequivalence by taking more numbers of healthy subjects, more sensitive analytical methods, and more advanced software for the calculation of the pharmacokinetic profile.

Abbreviations

T1: Test 1 (Zomelis); T2: Test 2 (Jalra); R: Reference (Galvus); DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide-1; GIP: Glucose-dependent insulinotropic polypeptide; HbA(1c): Glycated hemoglobin; FPG: Fasting plasma glucose; CDSCO: Central Drug Standard Control Organization; NS: Normal saline; BP: Blood pressure; C_{max}: Maximum plasma concentration; T_{max}: Time to reach peak plasma concentration; AUC: Area under the curve; ANOVA: Analysis of variance

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43094-021-00308-1.

Additional file 1.

Acknowledgements

Not applicable.

Authors' contributions

SS provided guidance during this study. MS performed the study and relevant work. MS was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board-DPSRU (ethics committee) registered with the DCGI as ECR/277/Indt/DL/2017 in its meeting. Informed consent form to participate in the study was also reviewed and approved by the ethics committee. The IRB-approved (ethics committee) informed consent to participate was taken from the participants in written form as per schedule Y of the Drug and Cosmetic Act 1945 (India). The informed consent was in English and vernacular language (Hindi). The study was described to each subject before their consent to participate in the study.

Consent for publication

Consent was taken from all participants to publish the research data of this study by concealing their personal identifiers.

Competing interests

The authors declare that they have no competing interests.

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Received: 12 December 2020 Accepted: 10 July 2021
Published online: 28 July 2021

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