Formulation and bioequivalence of two sildenafil 50 mg film-coated tablets after a single oral administration

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Original

Abstract. <u>Objective:</u> The aims of this study were to establish a bioanalytical method and to evaluate the bioequivalence of two drug products; a generic sildenafil 50 mg film-coated vs. the brand drug Viagra® 50 mg film-coated tablets. <u>Method:</u> Bioequivalence of tablets was tested by comparisons against the reference brand product in accordance with the requirements of the Declaration of Helsinki, the current Good Clinical Practice (GCP) Guidelines and the International Conference Harmonization (ICH). <u>Results:</u> The relationship between concentration and peak area ratio was found to be linear within the range of 1.435 – 410.023 ng/mL for sildenafil. The correlation coefficient (r) was always greater than 0.99 during the course of the validation. Statistical comparison of the main pharmacokinetic parameters showed no significant difference between test and reference. The 90% CIs of geometric mean ratios (test to reference ratios) were 99.656%, 99.806%, and 109.227% for AUC_{0-last}, $AUC_{0-\infty}$, and C_{max}, respectively. These pharmacokinetic parameter values lie within the FDA and European Medicines Agency specified bioequivalence limit (80 – 125%). Both formulations were well tolerated by all subjects and they were discharged in good health. <u>Conclusion:</u> The tested drug product was bioequivalent to the reference drug and had the same safety profile.

Introduction

Sildenafil, is chemically a 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H pyrazolo[4,3-d]pyrimidin-5-yl) phenyl-sulfonyl]-4-methylpiperazine (Figure 1). Sildenafil pH-value (strongest acidic and basic) is 7.27 and 5.97, respectively.

It was initially developed as an antihypertensive agent. It was approved by the U.S.
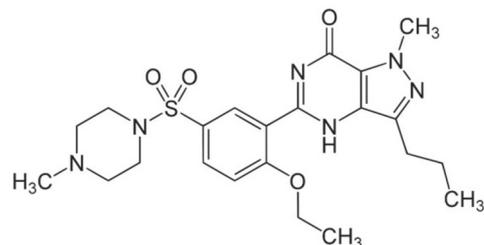
Food and Drug Administration (FDA) in 1998 as the first oral medication for the treatment of erectile dysfunction [1, 2]. Later, it was approved for pulmonary arterial hypertension [3]. The available data support the beneficial effects of sildenafil in improvement of tissue healing in various conditions [2], for lower urinary tract dysfunction [4], and even for preeclampsia [5] and Alzheimer's disease [6].

Sildenafil inhibits the conversion of cyclic guanosine monophosphate (cGMP) to guanosine monophosphate, thereby increasing the available concentration of cGMP. This reaction is largely catalyzed by the enzyme phosphodiesterase type 5. Sildenafil inhibits this enzyme, resulting in relaxation of smooth muscles. Sildenafil is absorbed rapidly, with peak plasma levels achieved within an hour. It undergoes hepatic metabolism and has a half-life of ~ 4 hours [1].

A patent was registered for this drug in 1990, which expired in 2010. Since expiration, the drug has been marketed under various trade names or as generic drugs [7]. The inactive ingredients for Viagra® in the tablet core includes microcrystalline cellulose, calcium hydrogen phosphate (anhydrous) croscarmellose sodium magnesium stearate, while the film coat includes the

Figure 1. Chemical structure of sildenafil.

hypromellose, titanium dioxide (E171), lactose monohydrate, and triacetin [8]. In the process of development of new generic formulation for a marked drug, the formulator tries to adhere to the same excipients used in the brand product in order to minimize any unexpected issues with stability. Additionally, the formulator attempts to find the level of excipient that minimizes in-vivo release differences. Accordingly, an in-vivo study is used to find any differences between the generic product and the original brand in terms of safety and clinical outcome.

In this paper a bioequivalence study was performed, where a bioanalytical method was validated and a comparative study between two drug products (sildenafil 50 mg film-coated tablets of (Avalon Pharma, Middle East Pharmaceutical Industries Co Ltd, KSA) vs. Viagra® 50 mg film-coated tablets of (Pfizer PGM, Zone Industrielle, Pocésur-Cisse, France) was designed and the key pharmacokinetic (PK) parameters for both drugs were assessed.

Materials and methods

The study was a comparative, randomized, two-period, two-treatment, two-sequence, single-dose, open-label, crossover bioequivalence study of a generic sildenafil 50 mg film-coated tablet vs. the brand drug Viagra® 50 mg film-coated tablet in healthy subjects under fasting conditions.

Volunteers and clinical protocol

The study was conducted by Arab Pharmaceutical Industry Consulting Co. Ltd./ Jordan in accordance with the requirements of the Declaration of Helsinki [9], the current Good Clinical Practice (GCP) Guidelines [10] and the International Conference Harmonization (ICH) [11] Guidelines. The study protocol and the informed consent forms were approved by the Institutional Review Board (IRB). Thirty adult male volunteers were recruited to participate in the study. The volunteers aged between 20 and 39 years, weighing between 57 and 93 kg with an average weight of 76 kg. The volunteers were subjected to a full medical and physical exam to confirm their healthy status and were not on any medication during the study period. A written informed consent, which explained the nature of the study, was given to the volunteers. The volunteers were instructed to abstain from taking drugs 1 month before the study initiation, caffeine and alcohol-containing beverages for at least 16 hours prior to each study drug administration and throughout the study period, fast for at least 10 hours before drug administration and no beverages except water, and no water for 1 hour prior to administration.

The study used an open-label, randomized two-period crossover design with a 7-day washout period between doses in 30 healthy subjects under fasting conditions. Prior to protocol generation, the number of subjects was determined using references on intra subject variability which does not need more than 28 subjects. The volunteers were randomly divided into two groups each of 15 subjects. The first group was given the reference brand and the second group was given the test formulation with a crossover after the washout period. The study was single center and subjects were confined till the last sampling time. During the wash out period they were away and they were back to the clinical site 16 hours prior to dosing of the second period. On the morning of the study, each volunteer gave a blood sample to serve as a blank for the drug assay. Each volunteer received an oral dose of the assigned formulation given with 240 mL of water in sitting position. During each period 22 blood samples; 8 mL 1 hour before dosing, and 8 mL samples were withdrawn at the following time points 0.17, 0.33, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, and 24.00 hours after dosing. A volume of 8 mL of blood was then placed in 10 mL heparin blood tubes and centrifuged (4,000 rpm for 5 minutes within max 15 minutes). Each plasma sample was transferred, using disposable polypropylene droppers into two labelled polypropylene tubes, then capped and stored in an Ultra freezer (–70 °C) until analysis. Four hours after drug administration a standard lunch meal containing soup (no carrots), 1/2 chicken, and rice with mixed vegetables was served and subjects had free access to water 1 hour after drug administration.

Chemicals

HPLC-grade methanol and Iso-propanol were from Scharlab S.L. (■■■ city, country?). Ammonium Acetate was from Merck KGaA, Damstadt, Germany. HPLC grade water was supplied by Carbon group (■■■ Full company name, city, country?). Diethyl ether was from JHD (■■■ Full company name, city, country?). Control human plasma (0.2 mL) was harvested from donors.

Instruments and chromatographic separations

The analysis was performed using an HPLC system (Agilent auto sampler model 1100) coupled with MS detector (Applied Biosystem, (■■■ city, country?) API Sciex 5000). The stationary phase was Luna 3u C18, 50×3.00 mm.

Preparation of standard solutions

Stock solutions of sildenafil were prepared by dissolving the drug in methanol. Working standard solutions were prepared from the stock solution by sequential dilution to prepare working solutions of sildenafil with concentrations of 275.975 ng/mL, 551.950 ng/mL, 827.775 ng/mL, 2,207.800 ng/mL, 7,885.050 ng/mL, 19,709.025 ng/mL, 31,540.200 ng/mL, 39,418.050 ng/mL, 47,310.300 ng/mL, 59,127.075 ng/mL, 70,965.450 ng/mL, and 78,850.500 ng/mL.

Sample preparations for HPLC injection

A volume of 0.200 mL plasma was harvested. A volume of 50 µL IS sildenafil-d_3 containing 1.085 µg/mL was added followed by vortex for 30.0 seconds. Sildenafil and the internal standard was extracted by adding 4.0 mL di-ethyl ether and shaking the fluid for 15.0 minutes. The mixture was centrifuged at a speed of 4,000 rpm to separate the 2 layers followed by decantation of 2 mL of the organic layer. The organic layer was evaporated under N2 (40 °C) and the residue was reconstituted with 1,000 µL mobile phase.

Validation procedures

The used analytical method was validated in the light of ICH Guidelines for linearity, precision, sensitivity, and recovery. During validation, for selectivity assays, 12 plasma batches were assessed including hemolized and hyperlipidimic. Moreover, part of the validation protocol was to assess some concomitant drugs like paracetamol, ibuprofen, caffeine and others. For sildenafil the linearity study was carried out in the range of concentrations from 1.435 to 410.023 ng/mL. The lower limit of quantitation (LLOQ) was estimated by analyzing known samples of sildenafil at progressively lower concentrations, starting at the lower end of the calibration curves. Accuracy and coefficient of variation (CV) were used to determine assay precision. Stock solution stability in mobile phase was assessed using two standard mixtures that are equivalent to LLOQ and the upper limit of quantitation (ULOQ). The internal standard concentration was 217.00 ng/mL. Short-term matrix based solution stability was assessed using plasma samples at quality control (QC) concentration of low and high. Samples were left at room temperature for 24 hours. Long-term matrix based stability was assessed using two quality control low (QCL) and quality control high (QCH) sildenafil concentrations which were stored at –70 °C and –20 °C. Auto-Sampler stability (injection phase) was assessed using six replicates of QCL and QCH. Stability after freeze and thaw cycles was also assessed using two sets of QC. Recovery for the drug and internal standard was assessed using six extracts at three concentrations. Matrix effect was investigated for sildenafil and the internal standard (Sildenfil-d3).

Pharmacokinetic and statistical analysis

The pharmacokinetics parameters were estimated using standard non-compartmental methods. The peak plasma concentration (C_{max}) and the corresponding time of peak plasma concentration (t_{max}) were taken directly from the data. The elimination rate constant (ke) was calculated from the slope of the semi-logarithmic plot of the terminal elimination phase of the plasma concentra-

Table 1. Summary of analytical parameters.

Full validation summary					
Parameter	Results				
Sensitivity	Accuracy of mean calculated concentration at LLOQ (96.45%). Precision of calculated concentration at LLOQ is (3.20%)				
Recovery	Analyte, mean recovery 100.78% (QCL), 105.72% (QCM), 113.39% (QCH). IS recovery = 88.31%				
Accuracy and precession	QC's	LLOQ	QCL	QCM	QCH
Within run (%)	Precision (CV %)	3.20	2.56	3.50	9.77
	Normalization	96.45	102.99	91.07	88.45
Between runs (%)	Precision (CV %)	7.90	8.67	3.82	6.60
	Normalization	100.07	104.83	94.17	91.16
Stability					
Short term stability(plasma)	Up to 24 h at (RT)				
Short term stability(stock solution in Mph)	Up to 23.00 h at RT (for sildenafil and sildenfil-d3)				
FTC stability	Up to 3 cycles at APIC ultra freezer (–70 °C). Up to 3 cycles at APIC freezer (–20 °C).				
Long term stability(stock solution in Mph)	Up to 35 days for Sildenafil and Sildenfil-d3 at APIC freezer (–20 °C)				
Long term stability (plasma)	Up to 78 days at APIC ultra freezer (–70 °C) Up to 78 days at APIC freezer (–20 °C)				
Post preparative stability	Injection phase	Up to 60 h at APIC freezer (–20 °C) Up to 59 h at auto-sampler temperature			
	Dry phase	Up to 60 h at APIC freezer (–20 °C)			
Whole blood stability	% of change between QCL and QCH = 6.00				
Matrix-dilution integrity	Samples above ULOQ (298.399 ng/mL) and up to 895.198 ng/mL can be diluted with dilution factor of 3				
Carry-over	No carry-over				
Matrix effect	CV% of the IS normalized (MF) was 4.62% and 3.73% for QCL and QCH, respectively				

tion-time curve calculated by linear regression. The elimination half-life time ($t_{1/2}$) was calculated using the formula $t_{1/2} = \ln2/ke$. The areas under the drugs plasma concentrations time curves from (AUC_{0-last}) and the area under curve to infinity ($AUC_{0-\infty}$) were calculated by using the linear trapezoidal method. Extrapolation to infinity was done by dividing the last measurable plasma concentration C_{last} by the terminal rate constant k_e ($AUC_{last\to\infty} = C_{last}/k_e$). The $AUC_{0\to\infty}$ is the sum of the estimated and extrapolated parts ($AUC_{0\to\infty} = AUC_{0\to last} + AUC_{last\to\infty}$). For the purpose of bioequivalence analysis, two way analysis of variance (ANOVA) was used to assess the effect of formulations, periods, sequences (fixed effects) and subjects (random effect) on AUC_{0-last}, $AUC_{0-\infty}$, and C_{max} using Thermo Scientific Kinetica (version 5.1), a commercially available Software package. As Kinetica cannot be used for the calculation of the 90% CI for the unbalanced design, SAS was used in the generation of the statistical report including the 90% CI for all pharmacokinetic parameters. As per the Food and Drug Administration (FDA) and the European Medicines Agency guidance for the conduction of the bioequivalence studies, the 90% CI for pharmacokinetic parameters C_{max} and AUC should lie within 80 – 125% [12, 13].

Results

Results of validation procedures

A summary of the validation parameters for the assay is provided in Table 1. Briefly, the relationship between concentration and peak area ratio was found to be linear within the range 1.435 – 410.023 ng/mL for sildenafil. The correlation coefficient (r) was always greater than 0.99 during the course of the validation.

The method was found sensitive with LLOQ of 1.435 ng/mL. Recovery of the drug ranged from 100.78 – 113.39%, recovery of IS was 88.31%. Short term matrix based stability proved that the drug is stable up to 24 hours at (RT).

Stock solution long term stability proved that the drug is stable up to 24 hours at (RT). Post preparative stability study showed that the drug is stable for 60 hours at dry and in-
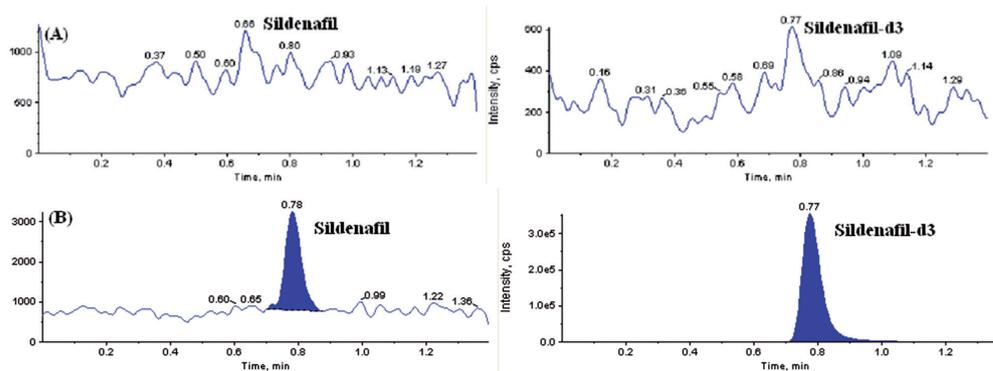
Figure 2. Representative chromatograms for an extract of (A) a blank plasma sample for Sildenafil, (B) extract of spiked plasma sample containing (1.435 ng/mL) at the (LLOQ) Sildenafil and Sildenafil-d3 (IS) (217.000 ng/mL) from a volunteer
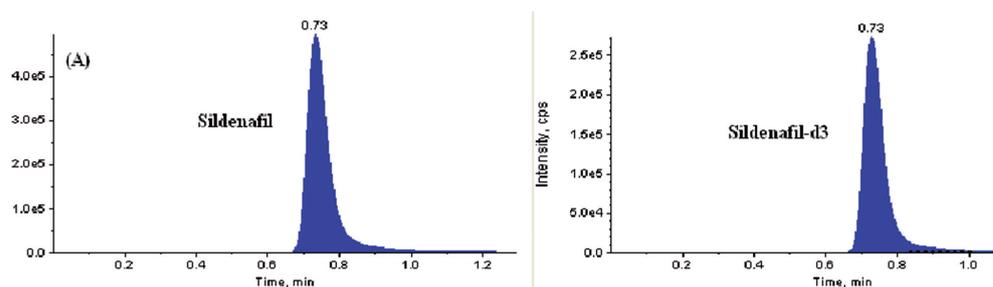

Figure 3. Representative chromatograms extract of plasma sample containing: (A) Sildenafil (298.399 ng/mL) (ULOQ) and Sildenfil-d3 (IS) (217.00 ng/mL) representing the C_{max} of a volunteer.

jection phase. Whole blood stability study proved that the drug is stable for 1 hour. Samples with concentration up to 895.198 ng/mL can be diluted with dilution factor of 3 with adequate accuracy and precision. No carry-over or matrix effect was found. Chromatograms of blank sample, LLOQ, C_{max} of a representative volunteer are presented in Figure 2 and 3.

Results of pharmacokinetic study

Both sildenafil 50 mg film-coated tablets of Avalon Pharma, Middle East Pharmaceutical Industries Co. Ltd, KSA, vs. Viagra® 50 mg film-coated tablets of Pfizer PGM, 37530 Pocésur-Cisse, France, were well tolerated by all the subjects and they were discharged in good health (One subject was excluded from the statistical evaluation but he was included in the assessment of safety). The only reported side effect was headache. Figure 4 shows plasma concentrations of both brands indicating that mean profiles after administration of the two formulations are superimposable. Figure 5 shows the individual overlays curves for plasma concentration for both tests and reference. The LLOQ is quite low and less than 3% of the C_{max} thus it is expected that the concentration after 16 or 24 will be detectable but it is very low. As per the statistical report there was no significant difference on the effect of period, sequence and formulation. All estimated PK parameters were in agreement with reported values. Table 2 shows a summary of the PK parameters for the two formulations of sildenafil 50 mg. As per the guidelines and the protocol of the clinical study, the 90% CI is calculated for all pharmacokinetic parameters. The 90% CIs of geometric mean ratios (test to reference ratios) were 99.656%, 99.806%, and 109.227% for AUC_{0-last}, $AUC_{0-\infty}$, and C_{max} respectively. No statistically significant difference between the two formulations was found. These PK parameter values lie within the FDA and European Medicines Agency specified bioequivalence limit (80 – 125%) [12, 13]. Our results in this part of the study suggest equivalent clinical efficacy of the two brands.
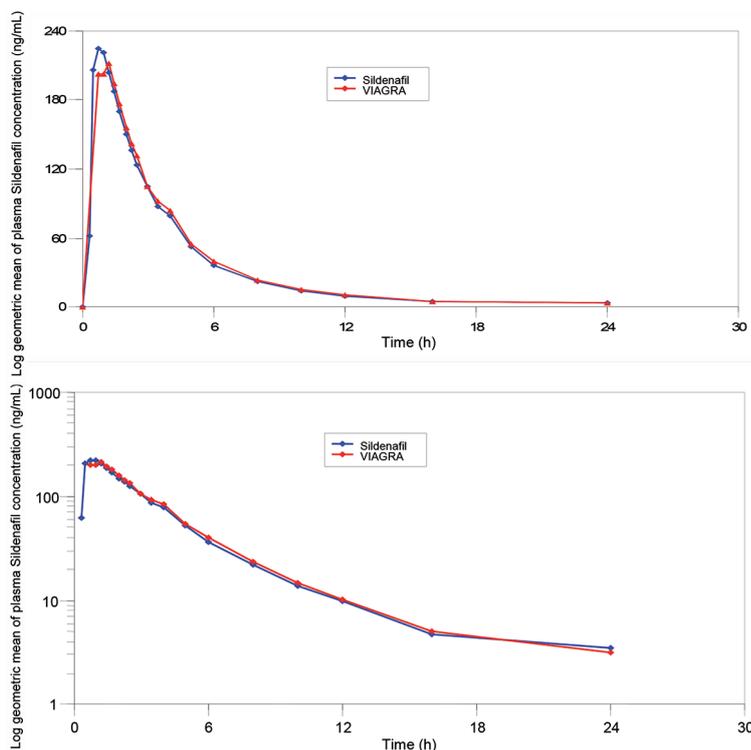
Figure 4. Plasma sildenafil geometric mean concentration (ng/mL) vs. time (h) curves (A) and log plasma sildenafil geometric mean concentration vs. time (h) curves (B) following a single oral dose sildenafil citrate 50 mg film-coated tablets.
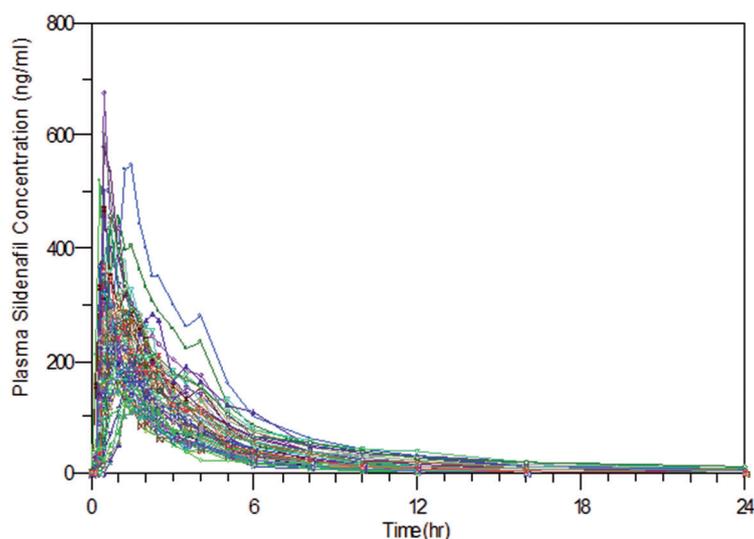

Figure 5. The individual overlays curves for plasma concentration for both tests and reference.

Discussion

According to The United States Food and Drug Administration (FDA), brand name drug is defined as a drug marketed under a proprietary, trademark-protected name and generic drug is the same as a brand name drug in active ingredient, dosage form, safety, strength, route of administration, quality, performance, intended use, and contains the same salt, ester, or chemical form. Generic versions of a drug can vary in shape, scoring configuration, packaging, and recipients. If all the previous criteria are met, then the two drugs are considered to be therapeutically equivalents [14].

During the development phase of an oral solid dosage form, several preformulation and formulation trials and tests are carried out in order to achieve a generic product that can be interchangeable with the original brand in terms of efficacy and safety. Accordingly, in-vitro dissolution in different pH media is conducted on the generic product and it must show similar dissolution profile or overlapping to the reference brand. In many cases these tests cannot replace the in-vivo tests which demonstrate the efficacy and safety of the generic product since it may contain different excipients.

Several previous studies have tested the bioequivalence of new generic sildenafil tablets [15] or other dosage forms as granules [16], disintegrated tablets [17] and chewable tablets [18]. The aim of this study was to test the bioavailability of sildenafil 50 mg tablets produced by Avalon Pharma, Middle East pharmaceutical industries Co ltd, KSA vs. the reference sildenafil 50 mg (Viagra®) produced by Pfizer PGM. The two dosage forms were administered to 30 fasting male volunteers in order to eliminate the influence of food on drug absorption.

The validated analytical methods described above were utilized for quantification of the plasma concentrations of sildenafil after administration of 50 mg of sildenafil as immediate release tablets. Analysis was successfully applied without interference with the used excipients in the tablet formulation. They provided the appropriate accuracy, sensitivity, and selectivity with high sample throughput and economically convenient procedure required for PK studies. In this study several PK were tested using a validated HPLC MS method. In fact, all validation parameters were conducted according to the international guidelines and they were within the accepted limits as reported in Table 1.

Table 2. Summary of calculated pharmacokinetic parameters of sildenafil in the bioequivalence study (n = 29).

PK parameters	Geometric mean	Minimum	Median	Maximum
Test sildenafil				
C_{max} (ng/mL)	306.353	119.475	300.561	676.830
$AUC_{0\rightarrow last}$ (ng×h/mL)	857.668	446.248	794.896	1,838.820
$AUC_{0\rightarrow\infty}$ (ng×h/mL)	877.657	462.140	814.228	1,888.290
t_{max} (h)	0.79	0.33	0.75	1.75
$t_{1/2}$ (h)	3.61	1.78	3.54	7.25
Reference Viagra®				
C_{max} (ng/mL)	279.741	119.310	283.087	577.143
$AUC_{0\rightarrow last}$ (ng×h/mL)	858.553	425.025	825.496	2,125.670
$AUC_{0\rightarrow\infty}$ (ng×h/mL)	877.396	430.930	836.007	2,168.030
t_{max} (h)	0.87	0.50	0.75	2.25
$t_{1/2}$ (h)	3.55	1.86	3.76	7.05
Parameter	Point estimate (Ratio of geometric mean%)	Lower limit %	Upper limit %	CV%
C_{max}	109.227	96.236	123.971	28.86558
$AUC_{0\rightarrow Last}$	99.656	92.634	107.209	16.43316
$AUC_{0\rightarrow\infty}$	99.806	92.791	107.350	16.38999

Regarding the efficacy of our generic product, statistical comparison of the main PK parameters, AUC_{0-last}, $AUC_{0-\infty}$, C_{max}, and t_{max} clearly indicated no significant difference between test and reference tablets, in any of the calculated PK parameters. The obtained values were compliant with the FDA and EMEA requirements for bioequivalence of generic drugs since the $AUC_{0-\infty}$, AUC_{0-last}, and C_{max} mean ratios are within the $80 - 125\%$ interval [12, 13]. It can be noticed that the C_{max} was higher for the test (676 ng/mL vs. 577 ng/mL) but still within the therapeutic range. The obtained PK parameters such as t_{max} and $t_{1/2}$ were comparable to previous similar studies that were conducted on volunteers from other races [15, 16, 17, 18]. It was concluded that the test tablets sildenafil 50 mg (film-coated tablet manufactured by Avalon Pharma) are bioequivalent for both extent and rate of absorption to the commercial Viagra® tablet (50 mg, Pfizer PGM) after single oral dose administration of each to healthy male adults under fasting conditions.

Safety is important also in our study all the volunteers that participated completed the study without showing any sign of adverse effect and were released in good health.

Conclusion

The statistical analysis of the results which performed on AUC_{0-last}, $AUC_{0-\infty}$, and C_{max} using the ANOVA method showed that both test tablets and reference tablets (Viagra® 50 mg) are bioequivalent, since they deliver equivalent quantities of active ingredient to the systemic circulation at equivalent rates for both AUC_{0-last} and C_{max} ratios within the $80 - 125\%$ interval proposed by FDA and the European Medicines Agency. The tested drug product was bioequivalent to the reference drug and had the same safety profile. This is important to achieve good therapeutic benefits and avoid potential problems which may arise due to poor formulation.

Conflict of interest

The authors report no conflicts of interest in this manuscript.

References

[1] *Viera AJ, Clenney TL, Shenenberger DW, Green GF*. Newer pharmacologic alternatives for erectile dysfunction. Am Fam Physician. 1999; *60:* 1159-1166., 1169, 1172

[2] *Farsaie S, Khalili H, Karimzadeh I, Dashti-Khavidaki S*. An old drug for a new application: potential benefits of sildenafil in wound healing. J Pharm Pharm Sci. 2012; *15:* 483-498.

[3] *Montani D, Chaumais MC, Savale L, Natali D, Price LC, Jaïs X, Humbert M, Simonneau G, Sitbon O*. Phosphodiesterase type 5 inhibitors in pulmonary arterial hypertension. Adv Ther. 2009; *26:* 813-825.

[4] *Uckert S, Oelke M.* Phosphodiesterase (PDE) inhibitors in the treatment of lower urinary tract dysfunction. Br J Clin Pharmacol. 2011; *72:* 197-204.

[5] *George EM, Granger JP.* Mechanisms and potential therapies for preeclampsia. Curr Hypertens Rep. 2011; *13:* 269-275.

[6] *Sabayan B, Zamiri N, Farshchizarabi S, Sabayan B.* Phosphodiesterase-5 inhibitors: novel weapons against Alzheimer's disease? Int J Neurosci. 2010; *120:* 746-751.

[7] *Leoni LA, Leite GS, Wichi RB, Rodrigues B.* Sildenafil: two decades of benefits or risks? Aging Male. 2013; *16:* 85-91.

[8] http://www.medicines.org.uk/emc/medicine/1474/SPC/Viagra+25mg,+50mg,+100mg/. ■■■last accessed?

[9] *World Medical Association.* (2008). "Declaration of Helsinki" as amended by the 59th World Medical Assembly. Seoul, South Korea.

[10] *European Medicines Agency* (1997). Note for guidance on good clinical practice (CPMP/ICH/135/95).

[11] International conference of harmonization of technical requirements for registration of pharmaceuticals for human use (1996). ICH harmonization tripartite guideline. Guidelines for good clinical practice.

[12] *Food and Drug Administration.* (2001). Guidance for industry: Statistical approaches to establishing bioequivalence. Available at: http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolutions.cfm?PrintAll=1. ■■■last accessed?

[13] *European Medicines Agency.* (2001). Note for guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98). London, UK.

[14] *Food and Drug Administration.* Glossary of terms. Available at: http://www.fda.gov/drugs/informationondrugs/ucm079436.htm. ■■■last accessed?

[15] *Kanjanawart S, Gaysonsiri D, Tangsucharit P, Vannaprasaht S, Phunikhom K, Kaewkamson T, Wattanachai N, Tassaneeyakul W.* Comparative bioavailability of two sildenafil tablet formulations after single-dose administration in healthy Thai male volunteers. Int J Clin Pharmacol Ther. 2011; *49:* 525-530.

[16] *Zheng R, Kim BH.* Pharmacokinetics and bioequivalence of sildenafil granules and sildenafil tablets in Korean healthy volunteers. Int J Clin Pharmacol Ther. 2014; *52:* 530-536.

[17] *Damle B, Duczynski G, Jeffers BW, Crownover P, Coupe A, LaBadie RR.* Pharmacokinetics of a novel orodispersible tablet of sildenafil in healthy subjects. Clin Ther. 2014; *36:* 236-244.

[18] *Marcelín-Jiménez G, Angeles-Moreno AP, Contreras-Zavala L, García-González A, Ramírez-San Juan E.* Comparison of fasting bioavailability among 100-mg commercial, 100-mg generic, and 50-mg chewable generic sildenafil tablets in healthy male Mexican volunteers: a single-dose, 3-period, crossover study. Clin Ther. 2012; *34:* 689-698.