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Relative Bioavailability of Chewable and Conventional Film-Coated Tablet Formulations of Sildenafil 100 mg in Healthy Volunteers Under Fasting Conditions

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Abstract

Pharmacokinetics and bioavailability of a chewable tablet formulation of sildenafil citrate 100 mg developed using taste-masking technology and taken with or without water (chewed until full disintegration and then swallowed) versus the conventional film-coated sildenafil tablet (Viagra®) taken with water were evaluated in the fasted state in a randomized, open-label, single-dose, 3-period crossover study in 30 healthy men aged 18 to 40 years (mean ± SD, 24±4 y). Sildenafil plasma concentrations were determined using a validated high-performance liquid chromatography method with ultraviolet detection. Bioequivalence criteria were 90% classic and Westlake CIs within 80% to 125% for test/reference ratios; limit tests applied were Schuirmann unilateral double *t* test and the Anderson-Hauck test. For area under the curve (AUC), bioequivalence criteria were met for all the treatments studied. For maximum plasma concentration (C_{max}), bioequivalence criteria were met for the chewable tablet with water relative to Viagra when using the Westlake CI. The chewable tablet without water had equivalent AUC, but the C_{max} was up to 22% lower when compared with Viagra or with the chewable tablet with water. Median time to C_{max} was lowest for the chewable tablet with water (0.75 h) versus Viagra (1.0 h) or the chewable tablet without water (1.75 h). Adverse events with the chewable tablet were consistent with the tolerability profile of Viagra. Only 1 (3%, chewable tablet with water) and 4 (13%, chewable tablet without water) subjects reported bitter taste, demonstrating successful taste masking.

Keywords: Bioavailability; Bioequivalence; Chewable; Dosage forms; Pharmacokinetics; Sildenafil

Abbreviations: AUC_{0-inf}: Area under the plasma concentration versus time curve from time 0 extrapolated to infinity; AUC_{0-t}: Area under the plasma concentration versus time curve from time 0 to time t; C_{max}: Maximum plasma concentration; K_e: Elimination rate constant; $t_{½}$: Elimination half-life; T_{max}: Time to reach C_{max}

Introduction

Sildenafil citrate is a phosphodiesterase type 5 inhibitor. In countries worldwide, including Mexico, sildenafil citrate is approved for the treatment of erectile dysfunction as conventional film-coated tablets of 50-mg and 100-mg strengths for oral administration with water (Viagra®, Pfizer Inc, New York, NY). Viagra is rapidly absorbed, reaching a mean maximum plasma concentration (C_{max}) of 514 ng/mL within 30 to 120 minutes (median, 60 min) after oral administration of the 100-mg dose in the fasted state [1]. Mean terminal half-life ($t_{½}$) is approximately 4 hours [1]. The absolute average bioavailability after oral administration is about 41% [1,2]. For doubling the dose, across the range of 25–200 mg, a small and clinically insignificant degree of non-proportionality was observed in predicted increases in C_{max} (2.1-fold) and in area under the plasma concentration versus time curve (AUC, 2.2-fold) [1].

A chewable tablet formulation of sildenafil citrate has been developed that does not have to be swallowed whole. Because citrate salts have a bitter taste, taste masking was essential to improve the palatability of the chewable tablet formulation.

The primary aim of this study was to evaluate the pharmacokinetics and bioavailability of sildenafil from its chewable tablet formulation taken with or without water relative to the marketed conventional film-coated tablet taken with water. Secondary objectives were to assess the tolerability and palatability of the new formulation.

Materials and Methods

Study design

This was a randomized, open-label, 3-period, 6-sequence, crossover trial in 30 healthy male volunteers aged 18 to 40 years, with body mass indices between 18 and 27 kg/m^2. Subjects were given single oral doses of the following 3 treatments after an overnight fast: Viagra 100-mg tablet with 250 mL of water; sildenafil citrate 100-mg chewable tablet with 250 mL of water, and sildenafil citrate 100-mg chewable tablet without water. Treatments were separated by 1-week washout periods between consecutive doses. Subjects were instructed to chew the chewable tablet until full disintegration and then swallow it, with or without water, depending on the treatment. Each subject was randomized to receive the 3 treatments in 1 of 6 possible sequences.

Health status was assessed based on physical examinations, medical records, electrocardiograms, and clinical laboratory results at

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the screening visit. Key exclusion criteria included use of prescription or nonprescription drugs, vitamins, or dietary supplements within 7 days or 5 half-lives (whichever is longer) before the first dose of study medication, except for acetaminophen at doses of ≤1 g/day; any clinically significant disease or drug allergies; febrile illness within the 5 days before first administration of study medication; sensitivity to heparin or heparin-induced thrombocytopenia; a positive test result for a drug of abuse; regular consumption of alcohol exceeding 14 drinks per week within the 6 months before the screening visit; excessive tobacco or nicotine use (equivalent to 5 cigars per day); an electrocardiogram showing QTc >450 msec at the screening visit; phosphodiesterase type 5 inhibitor use within the 4 days before first administration of the medicine under study; and treatment with nitrates or nitric oxide donors, either regularly or intermittently.

Blood samples were drawn from subjects before dosing and at 0.083, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, and 16 hours postdose in each treatment period. Samples were collected in 6 ml Vacutainer® tubes (BD Diagnostics, Franklin Lakes, NJ) using heparin as anticoagulant, then centrifuged at 4500 rpm for 5 minutes to separate the plasma. Plasma samples were transferred to two 2-mL polypropylene cryogenic tubes (labeled retention sample and analysis, respectively) and immediately stored at –70°C.

Plasma concentrations of sildenafil were determined at Investigación Farmacológia y Biofarmacéutica S.A. de C.V. (Mexico D.F., Mexico) using an in-house developed and validated high-performance liquid chromatography method with ultraviolet detection. The plasma samples were extracted using liquid-liquid extraction, propranolol was used as the internal standard, and separation was through a reverse-phase column. The analytical methodology was developed and validated according to the requirements of the Official Mexican Standard [3]. Validation of the method was shown by determination of stability of standard solutions and stability of analyte in biological fluid under conditions of processing and during the storage period, and by selectivity tests, accuracy tests, precision tests, calculation of the quantification limit, regression model, recovery, and validation of the quality-control samples in 3 levels of concentration (30 ng/mL [low], 1250 ng/mL [medium], and 2000 ng/mL [high]). The dynamic range of the assay was 10 ng/mL to 2500 ng/mL. During performance of the analytical runs, the percentage relative SD (% CV) of the quality control samples was ≤2.76% and the percentage relative error ranged from 2.23% to 8.29%, across the range of tested nominal concentrations.

Vital signs were assessed at 1, 2, 4, 6, 10, and 16 hours postdose. Safety was assessed through adverse event reports and changes in vital signs and clinical laboratory test results.

The design of this study complied with the provisions of the Official Mexican Standard [3]. The study was approved by the site's Ethics and Research Committee and conducted in accordance with the Declaration of Helsinki, Japan Revision, and with Good Clinical Practices. All volunteers provided written and verbal informed consent before study enrollment.

Statistical analyses

Noncompartmental pharmacokinetic analysis was performed using WinNonlin version 5.2 software (Pharsight Corporation, Mountain View, CA, USA), and the following pharmacokinetic parameters were calculated:

C_{max}: Maximum plasma concentration obtained graphically from the plasma concentration versus time profile

T_{max}: Time to reach C_{max} following drug administration, obtained graphically from the plasma concentration versus time profile

AUC_{0-t}: Area under the plasma concentration-time curve from time 0 (administration) to time t (last sampling time) calculated through the trapezoidal method

AUC_{0-inf}: Area under the plasma concentration-time curve from time 0 (administration) extrapolated to infinity

K_e: Terminal elimination rate constant

$t_{½}$: Elimination half-life, calculated as $Ln(2)/K_e$

Natural log-transformed AUC parameters (AUC_{0-t} and AUC_{0-inf}) and C_{max} of sildenafil were analyzed using a mixed-effect model with sequence, period, and comparator as fixed effects and subject within sequence as a random effect. Using geometric mean values, estimates of the adjusted mean differences (test – reference) and corresponding 90% CIs were obtained from the model. The adjusted mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of adjusted means (test/reference) and 90% CIs for the ratios. Comparisons were made between conventional oral Viagra (reference) and the chewable tablet with or without water (test).

The pharmacokinetic parameters AUC_{0-t}, AUC_{0-inf}, C_{max}, T_{max}, and $t_{½}$ of sildenafil were summarized descriptively by treatment. Mean profiles of the concentration versus time data were plotted by treatment.

The average bioequivalence statistics assessed the difference between the comparators administered orally, by a logarithmic comparison of the pharmacokinetic parameters C_{max}, AUC_{0-t}, and AUC_{0-inf}. A statistical analysis was made on the bioequivalence of the medicines based on the construction of classic and Westlake CIs, which result favorably to bioequivalence if the limits calculated fall within the pre-established interval from 80% to 125% for data logarithmically converted [4]. These data were analyzed with a 90% confidence level, with statistical power of >0.8.

Limit tests were based on the rejection of the null hypothesis of nonbioequivalence, to conclude, with an alpha significance level (0.05) and confidence level to 90%, that the comparators are bioequivalent. Limit tests applied were Schuirmann unilateral double *t* test and the Anderson-Hauck test on the quotient between average of comparator

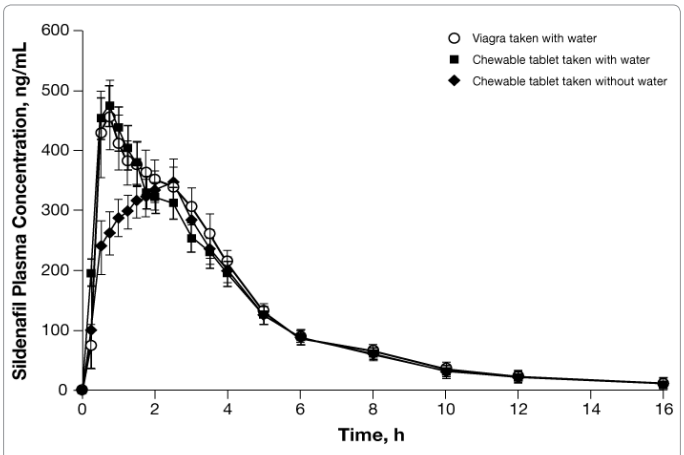

Figure 1: Mean (SE) plasma concentration over time for oral sildenafil 100 mg administered as Viagra taken with water, the chewable tablet formulation taken with water, and the chewable tablet formulation taken without water.

under study and comparator of reference, for pharmacokinetic parameters of C_{max}, AUC_{0-t}, and AUC_{0-inf} [5,6]. The limit test results would conclude bioequivalence if there was a <0.05 probability that the quotient is <80% and >125%.

Results

All 30 men who were enrolled completed the study. The mean ± SD age for the study population was 24.4±3.7 years (range, 20–35 y), mean weight was 69.9±7.6 kg, mean height was 170.5±7.0 cm, and mean body mass index was 24.1±2.2 kg/m^2.

Pharmacokinetics and bioequivalence

Mean sildenafil plasma concentration versus time profiles were nearly superimposable for Viagra and the chewable tablet taken with water; the chewable tablet taken without water resulted in a somewhat slower absorption rate, as indicated by lower C_{max} compared with the chewable tablets or Viagra taken with water (Figure 1). The sildenafil $t_{½}$ averaged approximately 2.9 to 3.5 hours and did not appear to be treatment dependent, particularly when the standard deviation is taken into consideration (Table 1). Median T_{max} was lowest for the chewable tablet taken with water (0.75 h) compared with Viagra (1.0 h) or the chewable tablet taken without water (1.75 h) (Table 1).

The classic and Westlake CIs (asymmetric and symmetric intervals around 100%, respectively) for logarithmically converted AUC_{0-t} and AUC_{0-inf} ratios were assessed as measures of the extent of systemic exposure. The intervals were contained within 80% to 125% for the chewable tablet taken with or without water, each compared with Viagra. Consistent with these statistical tests, the Schuirmann and Anderson-Hauck tests showed a high probability that AUC values fall within 80% to 125% (P<0.05), for which no statistically significant differences were found among the 3 comparators (Table 2).

For C_{max} ratios of chewable tablet taken with water compared with Viagra, the lower limit of the classic CI was <80% and the upper limit

	Viagra Conventional Film-Coated Tablet (n=30)	Chewable Tablet With Water (n=30)	Chewable Tablet Without Water (n=30)
T_{max}, h			
Mean (SD)	1.42 (0.95)	1.03 (0.68)	1.62 (0.80)
Median	1.00	0.75	1.75
CV, %	66.7	66.7	49.2
C_{max}, ng/mL			
Mean (SD)	657.64 (332.58)	556.75 (196.79)	517.46 (244.20)
Median	640.85	506. 92	448.80
CV, %	50.6	35.4	47.2
AUC_{0-t}, h•ng/mL			
Mean (SD)	1884.97(923.22)	1803.45 (859.73)	1680.04 (790.69)
Median	1668. 87	1571.24	1423.47
CV,%	49.0	47.7	47.1
AUC_{0-inf}, h•ng/mL			
Mean (SD)	1983.03 (1006.63)	1907.12 (978.50)	1797.13 (881.35)
Median	1744.81	1630.51	1502.24
CV,%	50.8	51.3	49.0
K_e, per h			
Mean (SD)	0.259 (0.094)	0.269 (0.079)	0.244 (0.094)
Median	0.252	0.282	0.252
CV,%	36.5	29.2	38.3
$t_{1/2}$, h			
Mean (SD)	3.06 (1.23)	2.94 (1.43)	3.45 (1.88)
Median	2.76	2.46	2.76
CV, %	40.1	48.7	54.6

AUC_{0-inf}=area under the plasma concentration vs time curve from time 0 extrapolated to infinity; AUC_{0-t}=area under the plasma concentration vs time curve from time 0 to time t; C_{max}=maximum plasma concentration; CV=coefficient of variation; K_e=elimination rate constant; $t_{½}$=elimination half life; T_{max}=time to reach C_{max}.

Table 1: Pharmacokinetic Variables for Sildenafil 100 mg.

Pharmacokinetic Parameter	Reference[a] Mean[b]	Test Mean[b]	Mean Ratio (%)	Classic CI (%)		Westlake CI (%)		Schuirmann Unilateral Double *t* (%)		Anderson-Hauck Test	Power
				Lower	Upper	Lower	Upper	Lower	Upper		
C_{max}, ng/mL											
CT with water	579.29	526.11	90.82	78.93	104.49	81.41	118.59	0.0680	0.0002	0.0678	0.8365
CT without water	579.29	455.55	78.64	68.35	90.48	70.54	129.46	0.5808	0.0000	0.5808	0.8365
AUC_{0-t}, h•ng/mL											
CT with water	1714.43	1663.47	97.03	90.94	103.52	92.18	107.82	0.0000	0.0000	0.0000	0.9999
CT without water	1714.43	1525.19	88.96	83.38	94.92	84.61	115.39	0.0041	0.0000	0.0041	0.9999
AUC_{0-inf}, h•ng/mL											
CT with water	1800.71	1752.02	97.30	91.50	103.46	92.67	107.33	0.0000	0.0000	0.0000	1.0000
CT without water	1800.71	1631.88	90.62	85.23	96.36	86.41	113.59	0.0006	0.0000	0.0006	1.0000
Criterion				≥80	≤125	≥80	≤125	<0.05	<0.05	<0.05	>0.8

CT=chewable sildenafil 100-mg tablet.
[a]Viagra conventional film-coated tablet.
[b]Least squares geometric mean.

Table 2: CIs and Limit Tests for Logarithmically Converted Pharmacokinetic Data.

was contained within 125%; the Westlake CI was contained within the bioequivalence limits of 80% to 125%. The Schuirmann test results for the lower limit were consistent with the classic CI results, whereas the Anderson-Hauck test failed to meet the established criteria. For the chewable tablet taken without water, both the classic and Westlake CIs were not contained within 80% to 125%; the C_{max} of the chewable tablet taken without water was about 22% lower than that of Viagra (Table 2).

Safety

A total of 17 adverse events were reported by 12 subjects following Viagra administration, 15 adverse events were reported by 13 subjects following chewable tablet administration with water, and 18 adverse events were reported by 13 subjects following chewable tablet administration without water. The most common adverse events that were considered probably related to the medicine were somnolence and headache (Table 3). Only a few of the 30 subjects in this study reported bitter taste with the chewable formulation (1 subject following administration with water and 4 subjects following administration without water; Table 3), indicating that unpleasant taste was successfully masked.

No statistically or clinically significant changes were noted in clinical laboratory test results compared with baseline values. Statistically significant decreases in systolic and diastolic blood pressure were recorded 1 to 4 hours after taking Viagra or chewable sildenafil with water and 4 to 6 hours after taking chewable sildenafil without water. These changes were not considered clinically meaningful.

Discussion

Administration of sildenafil 100 mg as conventional film-coated Viagra or a chewable tablet with water resulted in a similar pharmacokinetics, with rapid absorption (T_{max} within 1 h) and elimination ($t_{½}$ about 3–3.5 h). The peak and extent of systemic exposures for the 2 treatments were similar, with the 90% CIs of the test/reference ratios contained within 80% to 125%, establishing the existence of a fairly similar pharmacokinetic profile when administered with water. Chewable tablet taken without water showed a longer T_{max} (median prolonged by about 0.75 h) and lower C_{max} (mean reduced by about 22%), albeit with no statistically significant difference in the AUC, which means that the rate of absorption was slower but the total dose absorbed was equivalent. Therefore, for best results, it is recommended that doses of sildenafil citrate chewable tablet be taken with water. This may be particularly relevant for patients taking the 50-mg dose of sildenafil as the chewable tablet. For patients taking the 100-mg dose of the chewable tablet, the C_{max} reduction of about 22% when taken without water may not be clinically relevant because of the demonstrated efficacy of the 50-mg dose of Viagra, the standard recommended dose [7-9].

	Viagra Conventional Film-Coated Tablet	Chewable Tablet With Water	Chewable Tablet Without Water
Somnolence	9	6	7
Headache	7	6	7
Visual photosensitivity	1	1	0
Bitter flavor	0	1	4
Nausea	0	1	0

Table 3: Treatment-Related Adverse Events Associated With Sildenafil 100 mg (n=30 subjects).

Adverse events reported with chewable sildenafil were similar whether taken with or without water and comparable with those of Viagra. Oral sildenafil 100 mg, regardless of formulation, resulted in clinically insignificant decreases in systolic and diastolic blood pressure, an effect that is well documented with Viagra [10-12]. These changes were not considered clinically meaningful.

In conclusion, sildenafil citrate chewable tablet taken with water has a pharmacokinetic profile similar to the conventional film-coated tablet (Viagra) taken with water. When taken without water, the chewable tablet has somewhat lower C_{max} (reduced by about 22%), delayed T_{max} (1.75 h vs. 1.0 h), and equivalent AUC compared with Viagra taken with water. The taste-masking technology used in this formulation was successful in making the chewable sildenafil citrate formulation palatable. In this study in healthy volunteers, the sildenafil citrate 100-mg chewable tablet formulation was well tolerated, with reported adverse events that were consistent with the tolerability profile of Viagra.

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