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Pharmacological Study of Sildenafil on Healthy Volunteers

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Abstract

The present study is a comparative single-dose, open-label, randomized, three-treatment, six-sequence, three-period, crossover, *in vivo* study to determine the bioequivalence of two test products: Test 1; Sildenamax (Sildenafil 100 mg), Test 2; Satenafil (Sildenafil 100 mg) manufactured by Organo for Pharmaceutical and Chemical Industries, versus VIAGRA® (Sildenafil 100 mg) manufactured by Pfizer Egypt, USA and its Subsidiary in UK after a single oral dose administration given to healthy adult volunteers under fasting conditions. The subjects who conform to the study entry criteria were dosed according to a randomization schedule. Furthermore, the study was designed and completed according to the good clinical and laboratory practices.

Keywords: Pharmacokinetic parameters (C_{max}, T_{max}, K_e, AUC_{0-t}, and $AUC_{0-\infty}$); Sildenafil

Introduction

Sildenafil inhibits the cGMP-specific phosphodiesterase type 5 (PDE5) which is responsible for degradation of cGMP in the corpus cavernosum located around the penis. Penile erection during sexual stimulation is caused by increased penile blood flow resulting from the relaxation of penile arteries and corpus cavernosal smooth muscle. This response is mediated by the release of nitric oxide (NO) from nerve terminals and endothelial cells, which stimulates the synthesis of cGMP in smooth muscle cells. Cyclic GMP causes smooth muscle relaxation and increased blood flows into the corpus cavernosum. The inhibition of phosphodiesterase type 5 (PDE5) by sildenafil enhances erectile function by increasing the amount of cGMP [1,2].

To investigate the single-dose bioequivalence of test 2; Satenafil 100 mg Film-Coated Tablets manufactured by Organo for Pharmaceutical and Chemical Industries (Organo Pharma). For Helwan pharmaceutical (Sildenafil 100 mg) and VIAGRA® 100 mg Film-Coated Tablets manufactured by Pfizer Egypt S.A.E., Cairo, A.R.E. under License of Pfizer -Inc., USA and its Subsidiary in the UK (Sildenafil 100 mg) given to healthy adult males under fasting conditions. For the ln-transformed ratio (test product/reference product) for the bioequivalence parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) while other pharmacokinetic parameters of K_e, $t_{1/2}$, T_{max}, and (AUC_t/AUC_∞) % were reported. The influence of sequence, product, and period effect were tested by ANOVA [3,4]. Since drug formulation plays a key role in drug absorption, variations are expected from one formula to another for the same particular drug. Moreover, drug pharmacodynamics can be affected by its pharmacokinetics, which is invariably influenced by drug product formulation. All these necessitate the need for a biometric tool to prove the drug pharmaceutical equivalence or bioequivalence. Accordingly, the interchangeable use of bioequivalent products is justified and should afford the same therapeutic efficacy [5,6].

Ethics considerations

This research will be carried out in accordance with conditions stipulated by international clinical research guidelines and the principles enunciated in the Declaration of Helsinki resolved in Helsinki in 1964s and amended in Scotland, 2000; and the ICH harmonized tripartite guideline regarding Good Clinical Practice (GCP) adopted by the European Agency for the Evaluation of Medicinal Products. In addition, all local regulatory requirements will be adhered to, in particular, those which afford greater ion to the study of the participants (15) (Table 1).

No	Initials	*Gender	Age (years)	Weight (kg)	Height (m)	**BMI (kg/m^2)	*** Smoking	****Pregnancy
1	HMA	M	42	79	1.69	28	MS	NA
2	MAA	M	37	89	1.7	30.8	NS	NA
3	SMI	M	35	94	1.75	31	NS	NA

4	IAI	M	38	90	1.7	31.1	MS	NA
5	HZA	M	32	59	1.66	21.4	MS	NA
6	MSH	M	26	65	1.64	24	MS	NA
7	AES	M	26	87	1.64	29	NS	NA
8	AHA	M	30	59	1.68	21	MS	NA
9	MHM	M	32	70	1.77	22.4	MS	NA
10	SAM	M	21	52	1.64	19	MS	NA
11	SSA	M	28	84	1.78	27	NS	NA
12	IES	M	47	98	1.76	32	NS	NA
13	HMA	M	18	68	1.85	20	MS	NA
14	MAM	M	18	55	1.73	18	MS	NA
15	MHA	M	19	59	1.63	22	MS	NA
16	SFM	M	18	52	1.7	18	MS	NA
17	FMS	M	18	80	1.72	27	MS	NA
18	MAT	M	21	97	1.7	33.4	MS	NA

*M-male, F-female

**BMI is Body Mass Index, range 18 to 30 inclusive both (kg/m2)

***NS-Non-Smoker, MS-Moderate Smoker (less than ten cigarettes per day)

**** NA-Non Applicable

Physical Examination

Subject No.	Subject Initial	Kidney	Spine	Lymph nodes	Extremities	Neurological and reflex	Genitalia	Rectum	Mental status	Others
1	HMA	N*	N	N	N	N	N	N	N	N
2	MAA	N	N	N	N	N	N	N	N	N
3	SMI	N	N	N	N	N	N	N	N	N
4	IAI	N	N	N	N	N	N	N	N	N
5	HZA	N	N	N	N	N	N	N	N	N
6	MSH	N	N	N	N	N	N	N	N	N
7	AES	N	N	N	N	N	N	N	N	N
8	AHA	N	N	N	N	N	N	N	N	N
9	MHM	N	N	N	N	N	N	N	N	N
10	SAM	N	N	N	N	N	N	N	N	N
11	SSA	N	N	N	N	N	N	N	N	N
12	IES	N	N	N	N	N	N	N	N	N
13	HMA	N	N	N	N	N	N	N	N	N
14	MAM	N	N	N	N	N	N	N	N	N

15	MHA	N	N	N	N	N	N	N	N	N
16	SFM	N	N	N	N	N	N	N	N	N
17	FMS	N	N	N	N	N	N	N	N	N
18	MAT	N	N	N	N	N	N	N	N	N
* N- Normal results										

Table 1: Demographic characteristics and physical examination.

Inclusion criteria

Sex: Male

Age range between 18 and 55 years

Body Mass Index (BMI) of 18-30 (inclusive both) kg/m2 with a minimum of 50 kg weight.

The absence of evidence of any clinically significant deviation from the normal medical condition. Medical history and physical examination is performed within three weeks preceding the study start date.

Laboratory test results are within the normal ranges or deviation is dismissed as clinically-insignificant by the clinical investigator and the principal investigator. Laboratory tests are performed within six months preceding the study start date.

No history of allergy to the active or inactive ingredients in the products.

Volunteer willing to adhere to the protocol requirements and to provide written informed consent.

Methods and Procedures

Study Drug Administration: On study day 1 of each study period, the study drugs were administered according to a randomization plan.

Treatment 1: One Film-Coated Tablets Test 1 Sildenamax (Sildenafil 100 mg) taken with 240 mL of water (measured with a 100 mL cylinder) at room temperature [7,8].

Treatment 2: One Film-Coated Tablets Test 2 Satenafil (Sildenafil 100 mg) taken with 240 mL of water (measured with a 100-mL cylinder) at room temperature.

Treatment 3: One Film-Coated Tablets VIAGRA® (Sildenafil 100 mg) taken with 240 mL of water (measured with a 100-mL cylinder) at room temperature [9].

Bio-analytical drug determination methodology

In this study, a high-performance liquid chromatography (HPLC) method coupled with a mass spectrometer was used for analysis of Sildenafil in plasma and the results were satisfactory. The method was validated for selectivity, specificity, linearity, precision and accuracy, recovery, stability and dilution integrity according to USFDA guidelines (supplementary file)[10,11].

A high-performance liquid chromatographic (Shimadzu Prominence with rack changer) method coupled with mass spectrometric detection (LC-MS/MS(API4000)) was developed, optimized and validated at MRC laboratories for the determination of Sildenafil in human plasma. The method was fully validated according to the "FDA Bioanalytical Method Validation Guidelines 2003". The linearity of the assay method was verified within the concentration range of 25-2000 ng/ml. All results were within the acceptance criteria as stated in the recommended guidelines. The mean recovery of Sildenafil was 87.65% at 75 ng/mL, and 77.95% at 1500 ng/ml. The described method is proved to be sensitive, accurate and reproducible with a lower limit of quantification of 25 ng/mL for Sildenafil (Table 2) [12,13].

Item	Conditions
Column	x terra MS C18 4.5*50 mm, 3.5 µm
Column Temperature	Room temperature
Injection Volume	50 µl
Mobile Phase	70% Acetonitrile HPLC grade, 20% Ammonium formate 0.1 N,10% formic acid 0.1%
Flow Rate	0.55 ml/min
Detector	MS/MS
Internal Standard (IS)	Esomeprazole

Table 2: Chromatographic conditions and parameters.

Mass spectrometric conditions

The mass spectrometer was an API 4000+HPLC Prominence. The ion polarity was set in positive mode, and the source was TurboIon spray. The nebulizer gas was air (zero grade) and Nitrogen was the auxiliary, curtain, and collision gas (Tables 3 and 4).

Compound	Q1 Mass (Da)	Q3 Mass (Da)	CE (volts)	CXP (volts)	EP (volts)	DP (volts)
Esomeprazole (IS)	346.2	198.2	16.24	15	10	31.01
Sildenafil	474.9	100.3	40.28	17.86	10	127.96

Table 3: Mass spectrometric conditions.

Instrument	Prominence HPLC Shimadzu connected to Mass spectrometer API 4000, MDS Sciex, Toronto, Canada
Analytical Balance	BOECO BB1-31, 4-d, Germany, pre-use regular calibration was done daily.
Vortex	VWR VV3 S540 International West Charter-USA.
Centrifuge	Changsha Xiangzhi Instruments, Hunan, China
Vacuum Pump	TID-15, Apparao Garden, Choolai, Chennai, India.
pH meter	Corning pH meter, UK, the pre-application celebrative adjustment was done daily using standardized buffers of different pH-values (4.00-11.00).

Table 4: List of equipment used.

Statistical analysis

Statistical analysis was performed using a Kinetica version 5.1 (Thermo Scientific, USA).

The chemicals, reagents, and Standards used in the present study, are displayed as follows:

Sildenafil working standard

Esomeprazole working standard

Water for chromatography (Sharlau, Spain)

Acetonitrile, HPLC grade (Sigma Aldrich Chemie GmbH, Steinheim-Germany)

Ammonium Formate, Dichloromethane, (Sigma Aldrich Chemie GmbH, Steinheim-Germany)

Blank plasma obtained from the Holding Company for Biological Products & Vaccines (VACSERA), Giza, Egypt [14].

Statistical Results

Oral administration of Test 1; Sildenamax (Sildenafil 100 mg) and Test 2; Satenafil (Sildenafil 100 mg) to healthy adult volunteers at different interval time (0-24), as compared by the reference drug VIAGRA (Sildenafil 100 mg) to healthy adult volunteers at different interval time (0-24) showed that:

1. The rate and extent of absorption of Sildenafil through measurement of Sildenafil from, Satenafil 100 mg Film-Coated Tablets manufactured and VIAGRA® 100 mg.

2. The Test product, Satenafil (Sildenafil 100 mg) is bioequivalent to the reference drug VIAGRA® (Sildenafil 100 mg).

Therefore, the data obtained in this study prove, by appropriate statistical methods, the essential similarity of plasma levels of Sildenafil from the test product Satenafil 100 mg and from the reference product VIAGRA® 100 mg suggesting the equal clinical efficacy of these two products. The product, Satenafil 100 mg Film-Coated Tablets by Organo for Pharmaceutical and Chemical Industries (Organo Pharma) for Helwan pharmaceutical, may be used interchangeably with the reference product VIAGRA® 100 mg Tablets by Pfizer Egypt. That was shown the tested product has an acceptable therapeutic efficacy (Tables 5-18 and Figures 1-3) [15].

	0	2	4	6	12	24
Average	5.987133	346.6	134.7346	91.44	23.257	9.953833
STDEV	26.93952	213.1998	64.91686	62.50886	18.93988	28.67496

Table 5: Plasma concentration levels of Sildenafil (ng/mL) following administration of a single oral dose of treatment (2) test product Satenafil 100 mg.

	0	2	4	6	12	24
Average	7.920182	314.3067	130.1533	78.04333	21.75333	1.400167
STDEV	34.31167	147.4286	56.7114	39.54986	15.85234	1.906898

Table 6: Plasma concentration levels of Sildenafil (ng/mL) following administration of a single oral dose of Treatment (3) reference product VIAGRA® 100 mg.

Vol no.	Period	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng.h/mL)	AUC_{Ext} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	% AUC_{Ext}	K_e (h-1)	$t_{1/2}$ (h)
1	I	1120	1.5	1572.85	190.572	1763.42	10.807	0.1627	4.2605
2	I	660	1.25	1481.32	144.745	1626.06	8.9015	0.1934	3.5844
3	II	903	0.75	895.717	73.4119	969.129	7.5751	0.4461	1.5538
4	I	1060	1.5	1745.43	20.9461	1766.38	1.1858	0.1757	3.9442
5	III	447	2.5	1481.63	132.759	1614.38	8.2235	0.2164	3.2026
6	III	645	1.25	1439.18	6.9103	1446.09	0.4779	0.194	3.5723
7	III	702	1.25	2933.62	47.1775	2980.8	1.5827	0.1584	4.376
8	II	606	1.75	1228.02	213.055	1441.08	14.784	0.2399	2.8899
9	III	1000	2.5	3211	225.493	3436.49	6.5617	0.1055	6.5705
10	III	770	2.5	1719.41	23.3652	1742.77	1.3407	0.1643	4.2197
11	III	509	1.25	1008.72	8.2229	1016.94	0.8086	0.4071	1.7027
12	I	778	1.5	1106.96	41.3787	1148.34	3.6033	0.2694	2.5729
13	I	580	0.75	1093.32	12.9729	1106.29	1.1727	0.3736	1.8552
14	II	580	1.5	1331.2	37.1899	1368.39	2.7178	0.3292	2.1057
15	II	861	2	2721.47	13.9401	2735.42	0.5096	0.214	3.2384
16	I	421	1.25	1901.16	0.0739	1901.23	0.0039	0.4047	1.7129
17	II	831	2	2140.53	35.8445	2176.38	1.647	0.3508	1.9761
18	I	567	0.75	1097.68	7.6605	1105.34	0.693	0.2135	3.2464
19	III	1180	0.25	2457.13	11.112	2468.24	0.4502	0.2239	3.0951
20	I	905	1.75	1455.93	60.0267	1515.95	3.9597	0.2886	2.4015
21	II	459	2.5	1253.85	79.2279	1333.08	5.9432	0.2092	3.314
22	III	300	1.25	1101.85	73.1319	1174.98	6.2241	0.25	2.7729
23	II	451	1	1435.22	176.859	1612.08	10.971	0.1823	3.8017
24	II	414	0.75	1281.55	2.3033	1283.85	0.1794	0.2528	2.7418
25	III	372	0.5	865.9	40.2234	906.123	4.4391	0.2508	2.7641
26	II	360	0.5	847.342	42.3274	889.669	4.7577	0.245	2.8292
27	I	989	3	1608.8	166.496	1775.29	9.3785	0.1949	3.5559
28	II	594	0.25	2521.65	67.8498	2589.5	2.6202	0.137	5.0603
29	I	615	1	1877.6	4.933	1882.53	0.262	0.2405	2.8816
30	III	418	0.16667	2266.3	414.66	2680.96	15.467	0.0848	8.1702
Average		669.9	1.3556	1636.078	79.1623	1715.239	4.5749	0.2393	3.3324
STDEV		245.046	0.7492	632.5037	93.0308	658.0727	4.4464	0.0885	1.4083
CV%		36.5794	55.2674	38.6598	117.5191	38.3662	97.191	36.996	42.261

Table 7: Pharmacokinetic parameters of Sildenafil following administration of single oral dose of Treatment (2) test product Satenafil 100 mg to 30 volunteers.

Sl no.	Period	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (ng.h/mL)	AUC_{Ext} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	% AUC_{Ext}	K_e (h-1)	$t_{1/2}$ (h)
1	II	515	2.5	1909.58	106.39	2015.96	5.2774	0.2469	2.8078
2	III	495	2.5	1472.25	123.186	1595.44	7.7211	0.2229	3.1096
3	III	606	1.25	1190.05	79.9184	1269.97	6.293	0.3579	1.9368
4	III	774	0.5	1946.35	84.8929	2031.24	4.1794	0.2686	2.5803
5	II	508	1	1649.01	7.6936	1656.7	0.4644	0.2158	3.212
6	I	615	1.25	1449.6	8.6482	1458.25	0.5931	0.1851	3.7442
7	I	649	2	2363.52	8.389	2371.9	0.3537	0.2476	2.7998
8	III	769	1	1810.54	45.1567	1855.7	2.4334	0.3276	2.1158
9	II	501	1	1621.18	0.1068	1621.29	0.0066	0.4092	1.6937
10	I	487	2	1074.2	7.4244	1081.63	0.6864	0.4948	1.4009
11	II	396	0.75	552.493	28.0789	580.572	4.8364	0.3798	1.825
12	III	483	0.75	898.315	19.4081	917.723	2.1148	0.3031	2.2869
13	II	923	0.5	2007.56	15.5152	2023.08	0.7669	0.4343	1.5961
14	I	527	0.75	859.933	8.9968	868.93	1.0354	0.3941	1.7588
15	I	559	1.25	1784.62	73.332	1857.96	3.9469	0.2408	2.8781
16	II	621	1.75	1152.73	25.3576	1178.09	2.1524	0.3288	2.108
17	I	819	2	2763.83	1.6873	2765.52	0.061	0.3087	2.2457
18	III	549	1.25	1623.91	16.2142	1640.12	0.9886	0.1912	3.6252
19	II	428	0.75	1233.71	29.2673	1262.98	2.3173	0.1497	4.63
20	II	890	1.5	2507.91	433.555	2941.47	14.7394	0.0834	8.3117
21	III	393	1.5	922.326	45.6588	967.985	4.7169	0.2756	2.5151
22	I	326	1.25	1047.25	92.8824	1140.13	8.1466	0.1997	3.4705
23	I	344	0.25	1134.03	189.067	1323.1	14.2897	0.1679	4.1294
24	III	412	2	1395.34	19.4311	1414.77	1.3735	0.1805	3.84
25	II	925	2.5	1205.23	16.7845	1222.02	1.3735	0.4082	1.6983
26	III	1210	1.25	1278.77	25.7824	1304.55	1.9763	0.3039	2.2806
27	II	1200	0.25	2356.96	7.2764	2364.24	0.3078	0.2394	2.895
28	I	453	0.25	1600.44	1.5901	1602.03	0.0993	0.32	2.1662
29	III	983	1.75	1899.75	1.1175	1900.87	0.0588	0.3168	2.188
30	I	912	0.08333	1081.62	41.8158	1123.43	3.7222	0.2742	2.5283
Average		642.4	1.2444	1526.4336	52.1541	1578.5883	3.2344	0.2825	2.8126
STDEV		242.8532	0.7006	532.8043	84.4805	557.0102	3.8308	0.0939	1.3165
CV%		37.80405	56.2998	34.9052	161.9823	35.2853	118.4382	33.2382	46.8091

Table 8: Pharmacokinetic parameters of Sildenafil following administration of single oral dose of Treatment (3) reference product VIAGRA® 100 mg to 30 volunteers.

Time (h)	Satenafil 100 mg Film-Coated Film-Coated Tablets		VIAGRA® 100 mg Film-Coated Tablets	
	Average	± SD	Average	± SD
0	5.9871	26.9395	6.00841	30.609
0.833	11.3803	33.394	36.96	170.579
0.1667	58.0473	123.692	64.323	171.756
0.25	148.843	280.405	136.267	257.398
0.5	225.485	200.295	210.371	229.818
0.75	323.766	237.422	272.251	224.026
1	339.608	167.76	329.797	180.167
1.25	307.678	182.145	376.785	239.068
1.5	383.393	245.775	367.133	192.092
1.75	343.133	190.298	320.99	176.741
2	346.6	216.845	314.307	149.949
2.5	299.803	199.334	272.04	187.269
3	228.02	193.341	211.21	131.08
4	132.136	64.7913	130.153	57.6809
6	91.44	63.5775	78.0433	40.226
8	45.992	29.6938	44.771	25.6878
12	23.257	19.2637	21.7533	16.1233
24	9.9538	29.1652	2.5546	8.71318

Table 9: Plasma concentration Average ± SD (ng/mL) of Sildenafil following oral administration of Treatment (2) test product Satenafil 100 mg and Treatment (3) reference product VIAGRA® 100 mg to 30 volunteers.

	Test (B)			Reference (C)		
	Average	SD	CV%	Average	SD	CV%
C_{max} (ng/mL)	669.9	245.0456	36.5794	642.4	242.8532	37.804054
AUC_{0-t} (ng.h/mL)	1636.078	632.5037	38.6598	1526.4336	532.8043	34.9052
AUC_{Ext} (ng.h/mL)	79.1623	93.0308	117.5191	52.1541	84.4805	161.9823
$AUC_{0-\infty}$ (ng.h/mL)	1715.2394	658.0727	38.3662	1578.5883	557.0102	35.2853
AUC_{Ext}/ $AUC_{0-\infty}$	4.5749	4.4464	97.1908	3.2344	3.8308	118.4382
K_e (h-1)	0.2393	0.0885	36.996	0.2825	0.0939	33.2382
$t_{1/2}$ (h)	3.3324	1.4083	42.261	2.8126	1.3165	46.8091
T_{max} (h)	1.3556	0.7492	55.2674	1.2444	0.7006	56.29983

Table 10: Mean values of the pharmacokinetic parameters of Sildenafil derived from the plasma concentration-time profiles of treatment (2) test product Satenafil 100 mg and treatment (3) reference Product VIAGRA® 100 mg following single oral administration of 100 mg Sildenafil to 30 healthy volunteers.

	Point Estimate	Lower Confidence Limit	Upper Confidence Limit
C_{max} (ng/mL)	104.15%	90.08%	120.42%
AUC_{0-t} (ng.h/mL)	106.59%	95.12%	119.44%

$AUC_{0-\infty}$ (ng.h/mL)	108.12%	96.41%	121.25%

Table 11: 90% Confidence interval and point estimate for C_{max}, AUC_{0-t} & $AUC_{0-\infty}$.

	CV_{intra}
C_{max} (ng/mL)	0.052487
AUC_{0-t} (ng.h/mL)	0.036135
$AUC_{0-\infty}$(ng.h/mL)	0.036143

Table 12: Intra-subject variability for C_{max}, AUC_{0-t} & $AUC_{0-\infty}$.

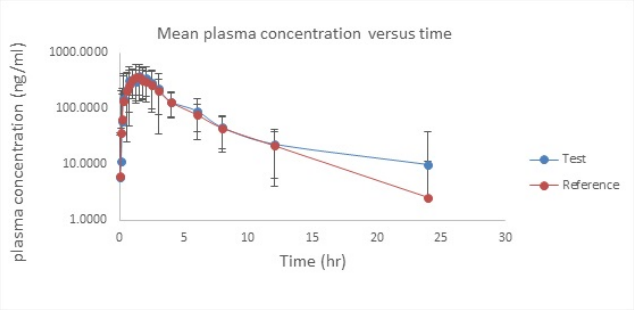

Figure 1: Mean plasma concentration *vs* time profile for Sildenafil after administration of an oral single-dose of 100 mg Sildenafil of the test product (Satenafil 100 mg) and the reference product (VIAGRA® 100 mg).

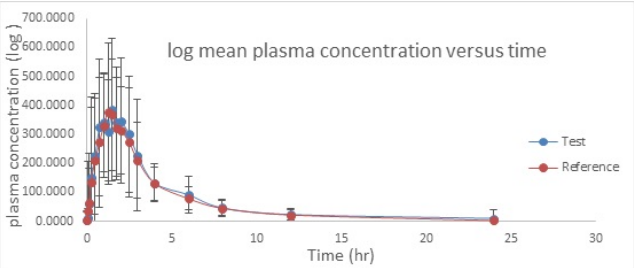

Figure 2: Logarithmic mean plasma concentration *vs* time profile for Sildenafil after administration of an oral single-dose of 100 mg Sildenafil of the test product (Satenafil 100 mg) and the reference product (VIAGRA® 100 mg).

Source	DF	SS	MS	F-Ratio	p-value	Significance
Period	2	0.015173	0.007587	0.06718	0.9351	Non-significant
Subject (Sequence)	29	3.7113	0.12798	1.133	0.337	Non-significant
Treatment	2	0.086264	0.043132	0.3819	0.6843	Non-significant
Error	56	6.3245	0.11294			
Total	**89**	**10.137**				

Table 13: ANOVA table with confidence interval for Ln C_{max}.

Source	DF	SS	MS	F-Ratio	p-value	Significance
Period	2	0.2718	0.1359	1.928	0.1549	Non-significant
Subject (Sequence)	29	6.1129	0.21079	2.991	0.0002173	Significant
Treatment	2	0.092849	0.046424	0.6587	0.5215	Non-significant
Error	56	3.9468	0.070479			
Total	89	10.424				

Table 14: ANOVA table with confidence interval for Ln AUC_t.

Source	DF	SS	MS	F-Ratio	p-value	Significance
Period	2	0.22616	0.11308	1.627	0.2056	Non-significant
Subject (Sequence)	29	6.0934	0.21012	3.024	0.0001904	Significant
Treatment	2	0.06778	0.03389	0.4877	0.6166	Non-significant
Error	56	3.8917	0.069495			
Total	89	10.279				

Table 15: ANOVA table with confidence interval for Ln AUC_{inf}.

Source	DF	SS	MS	F-Ratio	p-value	Significance
Period	2	0.55741	0.2787	0.5651	0.5715	Non-significant
Subject (Sequence)	29	12.045	0.41535	0.8421	0.6874	Non-significant
Treatment	2	0.91991	0.45995	0.9326	0.3996	Non-significant
Error	56	27.62	0.49321			
Total	89	41.142				

Table 16: ANOVA table with confidence interval for T_{max}.

Conc. %	Conc. (µg/mL)	Peak Area 1	Peak Area 2	Peak Area 3	Average Peak Area	SD	RSD (%)
25	25	262	262.1	264.8	262.95	1.59	0.60
50	50	522.1	526.5	526.3	524.94	2.48	0.47
75	75	806	808	811.9	808.64	3.04	0.38
100	100	1074.5	1075	1083.2	1077.56	4.88	0.45
125	125	1366.6	1363.4	1360.9	1363.64	2.81	0.21
150	150	1650.1	1639.2	1639.4	1644.67	7.7	0.47
200	200	2152.2	2158.1	2162.7	2157.66	5.24	0.24

Table 17: Average peak area response for different concentrations of sildenafil.

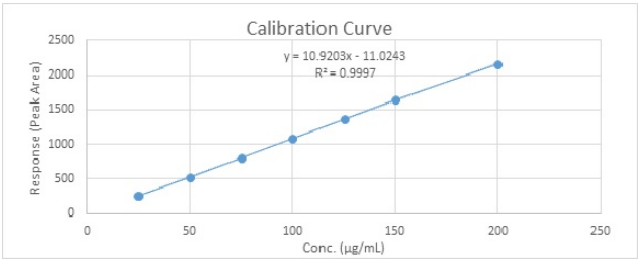

Figure 3: Response peak area versus concentration in µg/ml for calibration curve of test Sildenafil.

Regression line equation	y=ax+b
Slope, a	10.92
Intercept, b	-11.024
R^2	0.9997
LOD (µg/mL)	1.197
LOQ (µg/mL)	3.628
LOD (Limit of Detection)=	3.3 x δ (standard deviation)/Slope
LOQ (Limit of Quantitation)=	10 x δ (standard deviation)/Slope

Table 18: Results and stastistics.

Discussion

In this study, Satenafil 100 mg Film-Coated Film Coated Tablets, Batch no.:T30046 (Exp. date: 04/2018), manufactured by Organo for Pharmaceutical and Chemical Industries (Organo Pharma) for Helwan pharmaceutical, Egypt is bioequivalent to the reference product VIAGRA® 100 mg Film-Coated Tablets, Batch No.: 6702 (Exp. date: 01/2018) manufactured by Pfizer Egypt (Table 19).

90.08% -120.42% (104.15%)	for C_{max}
96.41% -121.25% (108.12%)	for AUC_t
95.12% -119.44% (106.59%)	for AUC_{inf}

Table 19: With an estimated 90% confidence interval (point estimate).

The present results showed that the two products are interchangeable and they deliver equivalent amounts of Sildenafil to the systemic circulation. In the current study, oral administration of Satenafil Film-Coated Tablets (Sildenafil 100 mg) to healthy adult volunteers were assessed for their ability to improve erectile dysfunction as same as VIAGRA Film-Coated Tablets (Sildenafil 100 mg) manufactured by Pfizer Egypt.

Conclusion

Bioequivalence could be demonstrated for Sildenafil within the prescribed 90% confidence interval of 80.00% to 125.00% for AUC_{0-t} and $AUC_{0-\infty}$ and for C_{max} to be within 80.00% to 125.00% with respect to the parametric method on Ln-transformed data.

The test product, Satenafil 100 mg Film-Coated Tablets by Organo for Pharmaceutical and Chemical Industries (Organo Pharma), investigated in this study was shown to be bioequivalent with the reference product; VIAGRA® 100 mg Film-Coated Tablets by Pfizer Egypt and its Subsidiary in the UK. Plasma levels may be used as surrogate parameters for therapeutic response. Therefore, the data obtained in this study prove, by appropriate statistical methods, the essential similarity of plasma levels of Sildenafil from the test product Satenafil 100 mg Film-Coated Tablets and from the reference product VIAGRA® 100 mg Film-Coated Tablets suggesting the equal clinical efficacy of these two products. The product, Satenafil 100 mg Film-Coated Tablets by Organo, may be used interchangeably with the reference product VIAGRA® 100 mg Film-Coated Tablets by Pfizer Egypt. That was shown the tested product has an acceptable therapeutic efficacy.

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