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ORIGINAL RESEARCH ARTICLE

Pharmacokinetics of a Novel Sildenafil Orodispersible Film Administered by the Supralingual and the Sublingual Route to Healthy Men

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Abstract

Background Sildenafil was the first selective drug available on the market as oral therapy for erectile dysfunction (ED). A novel sildenafil orodispersible film (ODF) for ED treatment, containing sildenafil citrate, has recently been marketed.

Objectives Study objective was to investigate sildenafil bioavailability of the novel ODF formulation after sublingual and supralingual administration.

Methods In this randomised, two-way cross-over study, 12 healthy male volunteers received a single 50 mg sildenafil dose by the sublingual and supralingual administration routes. Plasma sildenafil was determined up to 12 h post-dose. Peak concentration (C_{max}) and area under concentration-time curve (AUC_{0-t}) were calculated and compared between the two administration routes by analysis of variance (ANOVA).

Results Sublingual and supralingual administration can be claimed equivalent regarding the extent of sildenafil exposure since AUC_{0-t} 90 % CIs corresponded to 94.90–110.58% and were within the pre-specified acceptance range. C_{max} 90% CIs (79.92–125.57%) were only slightly outside the 80.00–125.00% limits, due to the small sample size, while the time to achieve C_{max} did not differ between treatments ($p = 0.9277$). Rate of exposure of the two administration routes was therefore similar. Reported treatment-related adverse events were mild to moderate headache (33.3% of subjects) and vomiting (8.3%).

Conclusions In healthy men, sublingual and supralingual administration of sildenafil ODF resulted in a remarkably similar pharmacokinetic profile and confirmed the safety of both study treatments. The recently marketed sildenafil ODF, administered by both investigated routes, can provide a valuable alternative to the marketed solid oral forms (tablets) in ED treatment.

Key Points

In healthy men, sublingual and supralingual administrations of sildenafil orodispersible film resulted in a remarkably similar pharmacokinetic profile and confirmed the safety of both study treatments.

The recently marketed orodispersible film, administered by both investigated routes, can provide a valuable alternative to the marketed solid oral forms (tablets) in erectile dysfunction treatment.

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1 Introduction

Penile erection is the result of smooth muscle relaxation in the penis. It includes arterial dilatation, trabecular smooth muscle relaxation, and activation of the corporeal veno-occlusive mechanism [1–3]. Erectile dysfunction (ED) is defined as the persistent inability to attain and maintain a penile erection sufficient to permit satisfactory sexual performance [1–3]. Phosphodiesterase type 5 (PDE5) is a regulator of vascular smooth muscle contraction in all smooth muscle districts and especially in penis, and PDE5 inhibitors are currently the first-line therapy for ED.

Sildenafil was the first selective inhibitor of cGMP-specific PDE5 available on the market as oral therapy for ED [2–6].

Sildenafil is rapidly absorbed, with maximum observed plasma concentrations (C_{max}) reached within 30–120 min (median time 60 min) after oral administration under fasting conditions. The mean absolute oral bioavailability is 41%

(range 25–63%). The area under the concentration–time curve (AUC) and C_{max} increase proportionally with the dose over the recommended oral dose range (25–100 mg) indicating a dose-proportional rate and extent of absorption. When sildenafil is taken after a heavy and fatty meal, the rate of absorption is reduced with a delay in t_{max} and a mean reduction in C_{max} by 29% [7, 8]. The mean steady-state sildenafil volume of distribution is 105 L, indicating distribution into the tissues. The total sildenafil body clearance is 41 L/h with a resultant terminal half-life ($t_{1/2}$) of 3–5 h. Sildenafil is cleared predominantly by the CYP3A4 (major route) and CYP2C9 (minor route) hepatic microsomal isoenzymes. The major circulating metabolite, resulting from N-demethylation of sildenafil, has a PDE selectivity profile similar to sildenafil and an in vitro potency for PDE5 approximately 50% of the parent drug. Plasma concentrations of this metabolite are approximately 40% of those found for sildenafil. The *N*-desmethyl metabolite is further metabolised, with a $t_{1/2}$ of approximately 4 h [9, 10]. The drug and its major circulating *N*-desmethyl metabolite are bound to plasma proteins in the amount of 96% and binding is independent of total drug concentrations [7, 11].

The good tolerability and safety profile of sildenafil for treating ED was established in approximately 74 double-blind placebo-controlled trials performed in more than 9000 patients, confirming that sildenafil is well tolerated at the recommended dose regimen. The most commonly reported adverse reactions in clinical studies among sildenafil-treated patients were headache, flushing, dyspepsia, nasal congestion, dizziness, nausea, hot flush, visual disturbance, cyanopsia and blurred vision. Adverse reactions from post-marketing surveillance have been gathered covering an estimated period > 10 years [12].

A novel sildenafil orodispersible film (ODF) containing sildenafil citrate has recently been marketed. The ODF formulation disintegrates rapidly in the oral cavity, usually within few minutes, without drinking or chewing, thus providing a valuable alternative to the marketed solid oral forms (tablets) in ED treatment. The ODF, available in 4 different dosage forms (i.e. 25, 50, 75 and 100 mg), obtained marketing authorisation in Switzerland and several European Countries in 2016 and has been very recently made available on the market.

In a previous single-dose, randomised, two-way cross-over Phase I study [13], the bioequivalence between the new Sildenafil IBSA 100 mg ODF, administered supralingually, and the marketed Viagra® 100-mg film-coated tablet, Pfizer Limited UK, was proven in terms of rate and extent of sildenafil absorption after single-dose administration [14]. In addition, no significant differences in sildenafil and *N*-desmethyl-sildenafil t_{max} values between the two products were observed, confirming that no significant sildenafil absorption differences occurred in the oral cavity after supralingual administration. However, due to its higher vascularisation with respect to the rest of oral cavity, the sublingual mucosa represents a specific route of absorption, that can possibly lead to modifications in the rate, extent or subject variability of drug absorption [15]. For this reason, in the present pilot study, the possibility of significant differences in sildenafil bioavailability after sublingual and supralingual administration of sildenafil ODF formulation was investigated. The pharmacokinetics of sildenafil *N*-desmethyl metabolite and the safety profile of the study treatments were also investigated.

2 Methods

2.1 Study Design and Procedures

The study protocol (code 17CH-SDF06) was approved by the Ethics Committee of Canton Ticino, Switzerland, and the Swiss Federal Health Authorities. All subjects were given a detailed description of the study and all gave written informed consent before enrolment. The study was performed in accordance with the Declaration of Helsinki and harmonised European standards for Good Clinical Practice (ICH E6 1.24), from November to December 2017.

The study was single-centre, single-dose, open, randomised, two-way cross-over and was designed according to the EMA guideline for bioequivalence studies [14].

The investigational product was sildenafil ODF, a thin, flexible, opaque, light blue, orodispersible film (IBSA Institut Biochimique S.A., Switzerland) containing 70.2 mg of sildenafil citrate, equivalent to 50 mg of sildenafil. It was orally administered in two study periods, below the tongue (tested alternative method of administration) and above the tongue (the approved method of administration of the product), with a wash-out interval of 6 days between administrations.

The study randomisation list was computer-generated by the Biometry Unit of CROSS Research S.A., Switzerland, using the PLAN procedure of the SAS/STAT® software version 9.3.

Subjects were confined at the clinical centre from the evening before administration up to 12 h post-dose and were in fasting conditions for 10 h before administration and up to 4 h post-dose. Water was allowed as desired, except for 1 h before and 1 h after dosing. In both study periods, the investigational product was administered on day 1 at 08:00 ± 1 h and under fasting conditions. The subjects took a standardised, small amount of still mineral water (20 mL) to moisten the oral cavity just before the ODF intake.

Thereafter, the investigator placed the investigational product either beneath the volunteer's tongue after folding the ODF once (sublingual route) or directly on the

volunteer's tongue, taking care not to fold the ODF (supralingual route). Once administered, after the film had dissolved completely (without chewing), the subjects could swallow saliva.

2.2 Subjects

Healthy male volunteers aged 18–45 years, with a body mass index of 18.5–30.0 kg/m^2, were enrolled in the study. All volunteers were in good physical health, as assessed through full physical examination, electrocardiogram (ECG) recording, vital signs measurement and clinical laboratory assays, according to the study inclusion criteria. No subjects were on abnormal diets or had a history of drug, alcohol, caffeine or tobacco abuse. Exclusion criteria included history or presence of significant diseases, history of vision or hearing problems related to drugs of the PDE5 inhibitor pharmacological class, history of priapism; anatomical deformation of the penis, history of ophthalmologic diseases and hypersensitivity or allergic reactions to sildenafil. Medications, including organic nitrates, were not allowed for 4 weeks before the study, while over-the-counter drugs and herbal remedies were not allowed for 2 weeks before screening. Subjects were not enrolled if they had participated in other clinical trials or donated blood in the past 3 months.

2.3 Blood Sampling

Blood samples for sildenafil and *N*-desmethyl-sildenafil measurements were collected at pre-dose (0) and 6, 15, 30, 45 min and 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h post-dose. Sampling time points were selected based on previously reported data [13].

Blood samples were collected using an indwelling catheter with switch valve. The cannula was rinsed, after each sampling, with about 1 mL of sterile saline solution containing 20 IU/mL Na-heparin. The first 2 mL of blood were discarded at each collection time to avoid contamination of the sample with heparin. The remaining 8 mL were collected from the catheter and transferred with a syringe into heparinised tubes (Li-heparin). The samples were stored on ice for a maximum of 20 min and then centrifuged at 4 °C for 10 min at 2500*g* to obtain plasma. Each plasma sample was immediately transferred into pre-labelled polypropylene tubes, and stored frozen at ≤ − 20 °C.

2.4 Bioanalytical Assay

Concentrations of sildenafil and *N*-desmethyl sildenafil in plasma were determined by a blinded analyst at Analytisch Biochemisch Laboratorium BV (ABL), the Netherlands, using a LC–MS/MS method developed and validated according to the requirements of the EMA and FDA guidelines on bioanalytical method validation [16, 17]. The method had a lower quantification limit (LQL) of 0.5 ng/mL and an upper quantification limit (UQL) of 2000 ng/mL for both analytes and adhered to the regulatory requirements for selectivity, sensitivity, precision, accuracy, recovery, carry-over, matrix effect, and stability.

Internal standards for the analysis were deuterated forms of the analytes (sildenafil-D_8 and *N*-desmethyl sildenafil-D_8).

Calibration standards for sildenafil and for *N*-desmethyl sildenafil in the range from 0.500 to 2000 ng/mL were prepared freshly in human Li-heparin plasma on the day of analysis.

Sildenafil and *N*-desmethyl sildenafil QC samples at the levels low (1.50 ng/mL), medium 1 (75.0 ng/mL), QC medium 2 (1000 ng/mL) and high (1600 ng/mL) were prepared in a batch and stored at ≤ − 18 °C prior to the start of the bioanalytical study.

Isolation of sildenafil, *N*-desmethyl sildenafil, sildenafil-D_8 and *N*-desmethyl sildenafil-D_8 from human Li-heparin plasma was performed by liquid/liquid extraction (LLE) with methyl *tert*-butyl ether. After extraction, the organic layer was evaporated to dryness under a gentle stream of nitrogen. The residue was reconstituted in injection solvent. Chromatographic separation was performed on a Waters XTerra MS C18 column using gradient elution. An API 4000 tandem mass spectrometry equipped with a turbo spray ionization source operating in the positive multiple reaction monitoring mode was used for quantification.

Data acquisition was performed using Analyst software (version 1.6.2) from AB Sciex. Following peak area integration, regression was also performed using Analyst. Concentrations were calculated using 13-point curves with weighted linear regression.

2.5 Pharmacokinetic Parameters

Pharmacokinetic parameters were determined or calculated using the validated software Phoenix WinNonLin® 6.3 (Certara, Inc). The primary study outcome measures were plasma sildenafil peak concentration (C_{max}), time to C_{max} (t_{max}) and area under the concentration–time curve up to the last sampling point (AUC_{0-t}) and extrapolated to infinity ($AUC_{0-\infty}$), calculated using the linear trapezoidal rule. The primary end-point of the study was the evaluation of the similarity of the two administration routes in terms of rate (C_{max} and t_{max}) and extent (AUC_{0-t}) of plasma sildenafil concentration. The following sildenafil pharmacokinetic parameters were also calculated: terminal volume of distribution (V_z/F), total clearance (Cl/*F*) and half-life ($t_{½}$). The same pharmacokinetic parameters were also calculated for the metabolite *N*-desmethyl-sildenafil, except for V_z/F and Cl/*F*.

2.6 Safety

The safety profile of the investigational product was assessed by evaluating treatment-emergent adverse events (AEs), physical examination, ECG, routine laboratory tests and vital signs checks. Vital signs (blood pressure and heart rate) were measured at screening, final visit, and on day 1 of each study period at pre-dose, 1.75, and 5 h post-dose. A 12-lead resting ECG was recorded at screening and final visit. Blood and urine samples were collected for routine haematology, blood chemistry, virology and urinalysis at screening and final visit. AEs were assessed throughout the study and were coded using MedDRA® version 20.1. A full physical examination was performed by the investigator at screening and at the final visit.

2.7 Sample Size and Statistical Analyses

Twelve healthy men were included in the study. The sample size was not based on any statistical evaluation, considering the exploratory purpose of the study.

The statistical analyses were performed using SAS® software version 9.3 (TS1M1) for Windows® and Phoenix WinNonLin® 6.3, Certara Inc.

A classical bioequivalence test was used for the comparison of sildenafil and *N*-desmethyl-sildenafil pharmacokinetic parameters [14]. Log-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were analysed by ANOVA, with treatment, period, sequence and subject-within-sequence as fixed effects. Similarity criterion was a geometric means ratio (PE) around 100 % and its 90 % confidence interval (CI) within the range 80.00–125.00%. Wilcoxon signed-rank test was used to analyse t_{max}.

3 Results

3.1 Subjects

Nineteen subjects were screened and twelve were randomised in the study. They received the treatment by the allocated route of administration, completed the study per protocol and were included in the pharmacokinetic and safety analyses. Demographic characteristics of the analysed subjects are presented in Table 1.

All subjects were in good physical and mental health, based on physical examination, medical and surgical history.

3.2 Pharmacokinetics

The mean ± standard deviation (SD) plasma concentration-time profiles obtained after sildenafil administration by the sublingual and supralingual routes are shown in Fig. 1 for sildenafil and in Fig. 2 for the *N*-desmethyl-sildenafil metabolite.

Table 1 Demographic data of study subjects ($N = 12$)

Parameter	Value
Sex, [n (%)]	
Male	12 (100.0%)
Race, [n (%)]	
Black	1 (8.3%)
White	11 (91.7%)
Age (years)	
Mean ± SD	36.2 ± 5.2
Range	23–45
Height (cm)	
Mean ± SD	176.9 ± 5.7
Range	167–187
Body weight (kg)	
Mean ± SD	79.5 ± 7.1
Range	68.5–88.4
Body mass index (kg/m^2)	
Mean ± SD	25.5 ± 2.9
Range	19.6–29.3

SD standard deviation

The main plasma pharmacokinetic parameters data (mean ± SD) and the results of their statistical comparisons are presented in Table 2 for sildenafil and in Table 3 for *N*-desmethyl-sildenafil.

Maximum plasma concentration (C_{max}) of sildenafil was 296.50 ± 142.69 ng/mL for the sublingual route (test) and 288.92 ± 118.78 ng/mL for the supralingual route (reference). The peak concentration was rapidly reached, at a similar median time for the two study treatments (i.e. 0.63 and 0.75 h for the test and reference treatments, respectively). Both the terminal volume of distribution and the total clearance (see Table 2) were almost the same for the two administration routes. Plasma concentrations declined rapidly after C_{max} with nearly identical half-lives, i.e. 2.55 ± 0.26 h and 2.69 ± 0.32 h for the sublingual and supralingual administration routes, respectively. AUC_{0-t} values were 761.72 ± 217.71 h•ng/mL for the test treatment and 750.76 ± 246.10 h•ng/mL for the reference. $AUC_{0-\infty}$ too was very similar for the two treatments, corresponding to 798.78 ± 227.68 and 793.44 ± 269.63 h•ng/mL for the sublingual and supralingual administration routes, respectively. The ratios of test/reference geometric means (point estimate, PE %) were 100.18, 102.44 and 102.13% for sildenafil C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, respectively, with their corresponding 90% CIs within the pre-specified acceptance limits for AUC_{0-t} (94.90–110.58%) and $AUC_{0-\infty}$ (94.58–110.29%)

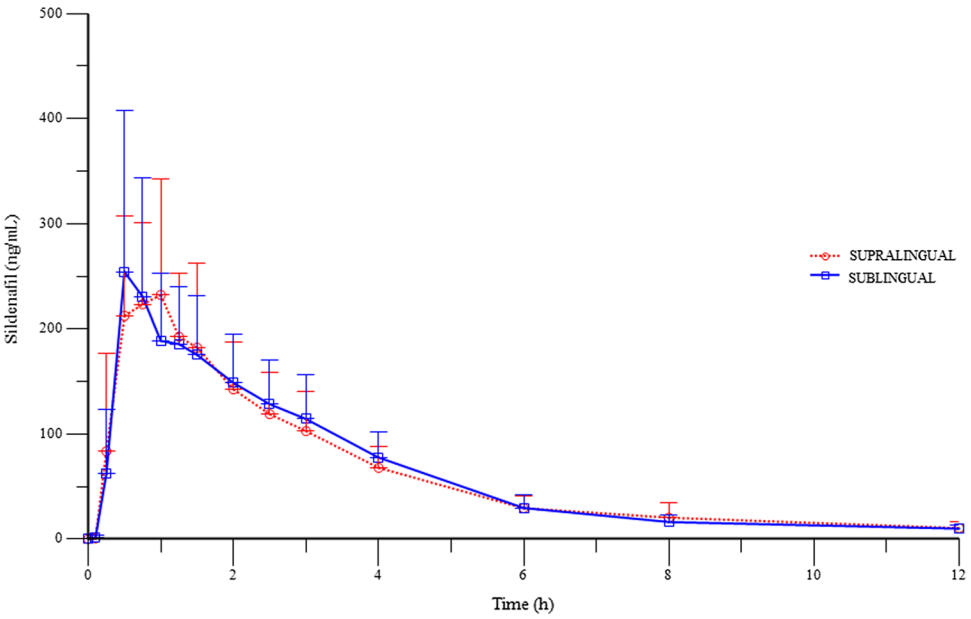

Fig. 1 Mean (+ SD) plasma sildenafil concentration (ng/mL) versus time profiles after single administration of sildenafil 50 mg orodispersible film by sublingual and supralingual route. Linear scale $N = 12$

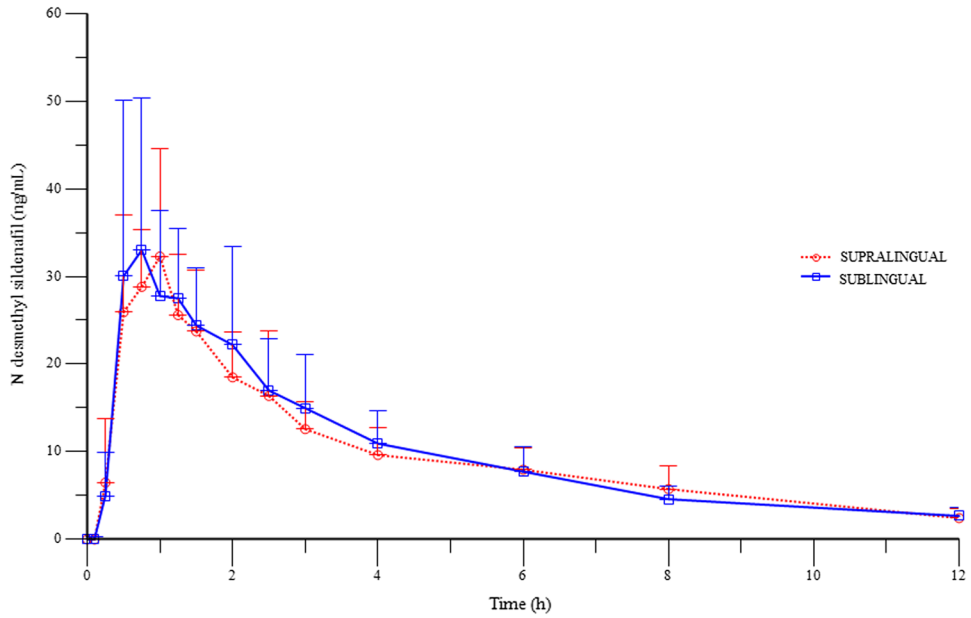

Fig. 2 Mean (+ SD) plasma *N*-desmethyl-sildenafil concentration (ng/mL) versus time profiles after single administration of sildenafil 50 mg orodispersible film by sublingual and supralingual route. Linear scale $N = 12$

and only just slightly outside the 80–125% range for C_{max} (79.92–125.57%).

N-desmethyl-sildenafil metabolite AUC_{0-t} and $AUC_{0-\infty}$ values were, on average, similar following administration of the two treatments (see Table 3) and their 90% CI fell within the limits of 80.00–125.00%. Extent of *N*-desmethyl-sildenafil exposure was therefore equivalent when the investigational product was administered sublingually and supralingually. After sublingual administration, *N*-desmethyl-sildenafil metabolite C_{max} was approximately 10% higher compared to the supralingual route (PE %: 109.75%). On the other hand, the metabolite t_{max} and $t_{½}$ were nearly identical for the two administration routes.

3.3 Safety

Both tested treatments showed a good safety profile and no serious AEs were reported. Four subjects (33.3%) reported mild-to-moderate headache and one subject (8.3%) experienced vomiting during the study. These AEs were deemed by the Investigator as possibly related to study treatments. No clinically relevant effects on vital signs, ECGs or laboratory parameters were observed.

Table 2 Sildenafil pharmacokinetic parameters and statistical analysis results after single administration of sildenafil 50 mg orodispersible film by sublingual and supralingual route $N = 12$

Sildenafil				
Pharmacokinetic parameter	Sublingual route (test)	Supralingual route (reference)	PE %	90% CI (%)
C_{max} (ng/mL), mean ± SD	296.50 ± 14 2.69	288.92 ± 118.78	100.18	79.92–125.57
t_{max} (h)[a], median (range)	0.63 (0.50–2.00)	0.75 (0.25–1.50)		
AUC_{0-t} (h•ng/mL), mean ± SD	761.72 ± 217.71	750.76 ± 246.10	102.44	94.90–110.58
$AUC_{0-\infty}$ (h•ng/mL), mean ± SD	798.78 ± 227.68	793.44 ± 269.63	102.13	94.58–110.29
V_z/F (L), mean ± SD	255.35 ± 107.88	266.46 ± 75.55		
Cl/*F* (L/h), mean ± SD	68.50 ± 23.90	70.87 ± 27.00		
$t_{½}$ (h), mean ± SD	2.55 ± 0.26	2.69 ± 0.32		

AUC_{0-t} area under the concentration–time curve from time 0 to the last observed concentration time t, *CI* confidence interval, *Cl/F* total clearance after oral administration, C_{max} maximum plasma concentration, *PE* ratio test/reference of geometric means, *SD* standard deviation, $t_{½}$ terminal half-life, t_{max} time to achieve maximum plasma concentration, V_z/F terminal volume of distribution after oral administration

[a]Comparison between sublingual and supralingual route by Wilcoxon signed-rank test: $p = 0.9277$

Table 3 *N*-desmethyl-sildenafil pharmacokinetic parameters and statistical analysis results after single administration of sildenafil 50 mg orodispersible film by sublingual and supralingual route $N = 12$

N-desmethyl-sildenafil				
Pharmacokinetic parameter	Sublingual route (test)	Supralingual route (reference)	PE %	90% CI (%)
C_{max} (ng/mL), mean ± SD	42.58 ± 17.20	37.38 ± 11.15	109.75	92.73–129.90
t_{max} (h)[a], median (range)	1.13 (0.50–2.00)	1.00 (0.50–2.50)		
AUC_{0-t} (h•ng/mL), mean ± SD	121.58 ± 33.17	117.69 ± 25.68	102.09	91.21–114.28
$AUC_{0-\infty}$ (h•ng/mL), mean ± SD	138.51 ± 38.22	133.73 ± 35.94	103.43	93.35–114.59
$t_{½}$ (h), mean ± SD	4.10 ± 1.37	4.07 ± 1.28		

AUC_{0-t} area under the concentration–time curve from time 0 to the last observed concentration time t, *CI* confidence interval, C_{max} maximum plasma concentration, *PE* ratio test/reference of geometric means, *SD* standard deviation, $t_{½}$ terminal half-life, t_{max} time to achieve maximum plasma concentration

[a]Comparison between sublingual and supralingual route Wilcoxon signed-rank test: $p = 1.0000$

4 Discussion

A sildenafil ODF containing sildenafil citrate has recently been marketed to meet the rising interest for sildenafil formulations able to dissolve very rapidly in the oral cavity without drinking or chewing, and to provide a more practical and user-friendly alternative to the marketed products for the treatment of ED.

Mean sildenafil plasma concentration-time profiles up to 12 h after single-dose sublingual and supralingual administration were nearly superimposable. The ratio of test/reference geometric means was very close to 100% for sildenafil C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, indicating a comparable rate and extent of sildenafil exposure with the two treatments. The 90% CIs were within the equivalence limits of 80.00–125.00% for the two AUCs and just slightly outside the pre-specified limits for the peak concentration, due to a high within-subject variability and the limited number of subjects in the study. The nearly identical t_{max}, volume of distribution, total clearance and $t_{½}$ values obtained with the two administration routes confirmed that sildenafil presented the same absorption, distribution and elimination kinetics after sublingual and supralingual dosing.

A comparison of the present results with the literature data [13], obtained after supralingual administration of the sildenafil 100 mg ODF during a bioequivalence study versus Viagra® 100 mg, showed similar rate and extent of exposure.

The data obtained in the present study and previously in the bioequivalence study between the ODF formulation and Viagra® film-coated tablets [13] indicated that the absorption of sildenafil in the mucosa of the oral cavity was negligible and had no significant impact on the drug kinetics.

After the complete dissolution of the ODF in the mouth, sildenafil was likely swallowed and absorbed further down in the gastro-intestinal tract, regardless of the place of disaggregation (sublingual or supralingual) of the film.

The 90% CIs for *N*-desmethyl sildenafil AUCs fell within the limits of 80.00–125.00%, and therefore the two administration routes were also equivalent with respect to the extent of metabolite exposure. The peak metabolite plasma concentration was slightly different between the two treatments, likely due to the small sample size considered. The sublingual route of administration showed a 10% higher C_{max} and, consequently, the 90% CI did not fall within the acceptance limits of 80.00–125.00%. However, the metabolite t_{max} and $t_{½}$ values were nearly identical ($p = 1.0000$) for the two administration methods, confirming that both the formation rate and the elimination rate of the metabolite were not significantly different. Considering that *N*-desmethyl sildenafil had a peak concentration less than 15% of its parent compound and 40% of its biological activity, the difference between the two administration routes in the metabolite C_{max} value can be considered clinically not significant.

Safety data confirmed a favourable safety profile of the investigational product, administered as single oral dose of 50 mg sildenafil by both the sublingual and supralingual routes.

The limited sample size (due to the exploratory nature of the study) did not permit to establish a formal bioequivalence between the two routes of administration, but the design and number of subject enrolled is deemed adequate by international guidelines [14] to obtain a reliable pharmacokinetic and statistical comparison between treatments.

5 Conclusion

In conclusion, in healthy men the sublingual administration of sildenafil 50 mg ODF produced the same pharmacokinetic profile as the supralingual administration. Study data confirm the similarity between the two routes of administration, thus suggesting that sildenafil ODF formulation, administered both sublingually and supralingually, can be an effective and safe treatment for ED.

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Complaince with Ethical Standards

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Conflict of interest V.F. is an employee of IBSA Institut Biochimique SA, L.L., C.L. and M.R. are employees of CROSS Research S.A., which was contracted by IBSA Institut Biochimique SA as CRO for the conduction of this study and received financial support for its services. The authors declare that they have no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval The study protocol (code 17CH-SDF06) was approved by the Ethics Committee of Canton Ticino, Switzerland, and the Swiss Federal Health Authorities.

Informed consent All subjects provided written informed consent before enrolment.

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