

Sticking to therapy: bioequivalence assessment and adhesion performance of rivastigmine transdermal patch formulations

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Abstract

Background: Rivastigmine transdermal drug delivery systems (TDDS) provide smoother plasma concentration profiles and improved tolerability compared with oral formulations.

Methods: This study aimed to evaluate the bioequivalence, adhesion performance, and safety profile of a branded generic rivastigmine TDDS, Rivazich (13.68 mg, 9.5 mg/24 h) compared with the reference product, Exelon Patch 10 (18 mg, 9.5 mg/24 h) following a single 24-hour application in healthy subjects. In an open-label, randomized, two-period crossover trial conducted under fasting conditions, 74 subjects were enrolled and 58 completed the study. Plasma concentrations of rivastigmine were quantified using a validated HPLC–MS/MS method up to 48 h post-dose. Noncompartmental analysis was performed to derive $C_{\max}$, AUC_{0-t} , and partial AUCs (0–12 h and 12 h–t) for bioequivalence assessment. Adhesion performance was evaluated at predefined time points, and non-inferiority at 24 h was assessed using a –10% margin, in accordance with regulatory guidance.

Results: The 90% confidence intervals for all pharmacokinetic parameters were within the predefined bioequivalence acceptance range of 80–125%. Adhesion analysis demonstrated non-inferiority of the test formulation.

Conclusions: According to the regulatory requirements, the test and reference formulations were considered bioequivalent.

Trial registration: ClinicalTrials.gov, NCT07464340. Registered 11 March 2026 - Retrospectively registered, <https://clinicaltrials.gov/study/NCT07464340>

Key Points

- The branded generic rivastigmine patch delivers the same therapeutic dose through a smaller patch area with a superior delivery efficiency, and was well tolerated, supporting its therapeutic interchangeability with the reference product.
- The branded generic rivastigmine patch (13.68 mg / 9.5 mg/24 h) was bioequivalent to the reference drug product (18 mg / 9.5 mg/24 h) in healthy subjects, with all 90% confidence intervals for C, AUC, AUC, and AUC within the 80–125% acceptance range; adhesion non-inferiority was also demonstrated.

1. Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disorder characterized by progressive impairment of the cortically projecting cholinergic system (Davies and Maloney 1976). The resulting deficiency in acetylcholine (ACh), a primary neurotransmitter that facilitates learning and attention, leads to significant cognitive, behavioral, and functional decline. Cholinesterase inhibitors remain the cornerstone of symptomatic treatment across the clinical spectrum of AD (Jann et al. 2002). Among

these, rivastigmine acts as a slowly reversible, centrally selective dual inhibitor of acetylcholinesterase and butyrylcholinesterase. Its efficacy in improving cognition, activities of daily living, and global function is well-established in both AD and Parkinson's disease dementia (United Medical LTDA.).

While dose-response relationships suggest that higher enzyme inhibition yields greater clinical benefits, the utility of oral cholinesterase inhibitors is often limited by gastrointestinal (GI) adverse effects, which are largely driven by rapid increases in peak plasma concentrations (C_{max}) and short times to peak t_{max} following oral intake. To address these limitations, rivastigmine was developed as a TDDS (Kurz et al. 2009; Khoury et al. 2018). By providing continuous drug delivery over 24 hours, the transdermal route minimizes peak-to-trough fluctuations, delays t_{max} , and significantly lowers C_{max} compared to capsules, while maintaining similar overall exposure (Winblad et al. 2007a). Clinical trials, such as the IDEAL study, have demonstrated that this smoother pharmacokinetic profile translates into improved tolerability, allowing patients to access higher therapeutic doses with fewer GI side effects compared to the oral regimen (Winblad et al. 2007b).

The pharmacokinetic profile of rivastigmine patches is characterized by a slow absorption phase with a median t_{max} typically ranging between 10 and 16 hours in healthy volunteers. Previous single-dose investigations have highlighted the influence of application site and body weight on exposure, while showing no clinically relevant ethnic differences between Japanese and Caucasian subjects (Lefèvre et al. 2007). Despite these advantages, the physical performance of the patch—specifically adhesion—remains a critical variable, as detachment can alter drug flux and compromise therapeutic efficacy (FDA 2021; Schurad et al. 2022).

Although the clinical utility of rivastigmine patches is proven, most published regulatory bioequivalence studies have focused on multiple-dose administration under steady-state conditions (Morte et al. 2022). Single-dose characterization is important for detecting potential differences in the initial drug release phase and skin permeation kinetics, factors that might be masked by drug accumulation at steady-state. Furthermore, demonstrating bioequivalence in a single-dose design serves as a rigorous test of a brand generic formulation performance regarding adhesion, drug flux, and absorption rate before steady-state concentrations are achieved (FDA 2019; EMA 2014; ANVISA 2022).

Therefore, the present study aims to fill this gap by evaluating the bioequivalence, adhesion performance, and safety profile of a new rivastigmine patch generic formulation (13.68 mg – 9.5 mg/24 h) compared to the reference product Exelon[®] Patch 10 (18mg – 9.5 mg/24h) following a single 24-hour application in healthy subjects.

2. Materials and Methods

2.1. Ethical Aspects

Instituto de Ciências Farmacêuticas de Estudos e Pesquisas (Goiânia, Goiás, Brazil), a certified bioequivalence center in Brazil, conducted all phases of this clinical trial. The study protocol was approved by the Research Ethics Committee at Instituto de Ciências Farmacêuticas de Estudos e Pesquisas (Goiânia, Goiás, Brazil), with protocol number 5.999.355 approved on April, 13rd 2023 (Trial registration: ClinicalTrials.gov, NCT07464340, registered 11 March 2026 - retrospectively registered, <https://clinicaltrials.gov/study/NCT07464340>). All study details, including objectives, procedures, potential benefits and risks, and the voluntary nature of participation were thoroughly explained to all participants. Informed consent was obtained from all participants before any study-related activities. The study adhered to the International Council for Harmonization (ICH) Guidelines for Good Clinical Practice (ICH E6) (International Council for Harmonization (ICH).), ethical principles outlined in the Declaration of Helsinki (World Medical Association 2013) and CONSORT guidelines (Hopewell et al. 2025). Additionally, this study meets the requirements for clinical and bioequivalence assessment of the Brazilian Health Regulatory Agency (ANVISA) (ANVISA 2022).

2.2. Study Design and Population

In order to evaluate bioequivalence and adhesion performance, this study was performed in a single center, with an open-label, randomized, balanced, crossover, single-dose design, including two treatment regimen, two periods, and two administration sequences (2 x 2 x 2). Participants received either the test or the reference product under fast conditions, with a 7-day washout period, selected based on participant convenience and literature-reported elimination half-life for rivastigmine of 4 hours (United Medical LTDA.).

The protocol applied stratified randomization with block allocation to ensure sex balance. Each block allocation represented a participant who received both formulations in 2 distinct periods, with randomized sequences and evenly assigned. This approach minimizes the potential impact of sequence and period effects on the outcomes.

The study design accounted for a desired statistical power of 80% for bioequivalence and adhesion studies. A within-subject coefficient of variation (CV_{ws}) of up to 35% was considered for the primary parameters, based on previously published rivastigmine transdermal studies conducted under a crossover design, in which CV_{ws} values ranged from 16% to 68% (FDA 2007; Lefèvre et al. 2007). The expected geometric mean ratio between treatments ranged from 95% to 105%. The sample size calculation also accounted for possible dropouts and exclusions to ensure reliable statistical outcomes.

The enrollment included 74 healthy participants (38 men and 36 women) aged 18–50 years and body mass index (BMI) between 18.5 and 30.0 kg/m². The inclusion criteria encompassed distinct health and eligibility features; participants had to demonstrate good overall health status, which the medical researcher assessed by reviewing medical histories, vital signs, anthropometric measurements, physical examinations, electrocardiogram results, and laboratory tests. Furthermore, participants also had to be asymptomatic, and either be fully vaccinated against COVID-19 or show no evidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by quantitative reverse transcription

polymerase chain reaction (RT-qPCR) or rapid antigen testing before each admission. Participants with skin markings, such as pigmentation issues, scars, excessive hairiness, or tattoos in the patch application area were excluded since it may interfere with the patch’s adhesion performance and, consequently, the drug absorption. In addition, to ensure the safety of participants, they had to agree to use an effective form of contraception.

2.3. Patch formulations

The test formulation was Rivazich[®], a rivastigmine transdermal patch containing 13.68 mg (nominal delivered dose 9.5 mg/24 h), batch No. 25779, expiry date August 2024, manufactured by Amarin Technologies S.A. (Buenos Aires, Argentina) and imported by Adium S.A. (São Paulo, Brazil). The reference formulation was Exelon[®] Patch 10 (batch No. ALT345230, expiry date July 2023), a rivastigmine transdermal patch containing 18 mg (nominal delivered dose 9.5 mg/ 24 h), manufactured by Lohmann Therapie-Systeme AG (Andernach, Germany) and imported by United Medical Ltda. (São Paulo, Brazil). Before the *in vivo* study, *in vitro* assays were conducted with the same batches to guarantee the pharmaceutical equivalence and release profile similarity of both products.

Prior to the bioequivalence/adhesion clinical study, pharmaceutical equivalence between the test and reference transdermal patches was assessed using *in vitro* quality tests in accordance with regulatory recommendations for transdermal delivery systems (ANVISA 2010). These evaluations included visual and dimensional characterization (appearance, patch size and surface area), matrix weight determination, uniformity of dosage units, drug content and identification, impurity profile, residual solvents, and *in vitro* drug release (dissolution profile) assessments. All results complied with the predefined acceptance criteria and confirmed the pharmaceutical comparability of the batches used in clinical study. Detailed results are not presented due to proprietary considerations but are available in the regulatory dossier submitted to the Brazilian regulatory authority.

It is important to note that the test formulation is a square patch with rounded corners (7.6 cm²), whereas the reference formulation is a rounded patch (10.0 cm²), as detailed in Table 1 and Fig. 1.

Table 1
Characteristics of patch formulations used in the study.

Characteristic	Test	Reference
Drug content (mg per patch)	13.68	18.00
Dose delivered (mg/24h)	9.5	9.5
Patch delivery efficiency (%)	69.4	52.8
Patch area (cm ²)	7.6	10.0
Patch Area Activity (%)/cm ²	9.14	5.28

As per European Medicines Agency (EMA) Guideline on Quality of Transdermal Patches, Patch Area Activity (PAA), expressed in $\%/cm^2$ represents a measure of the formulation's intrinsic capability to release the active substance from the patch *in vivo* and therefore serves as a surrogate measurement of thermodynamic activity (EMA 2014). A higher PAA reflects greater efficiency in delivering the drug per unit area. It is an indirect tool to determine the appropriateness of formulation development for a generic transdermal patch by putting two major product development parameters into relation: patch area and overall amount of active substance necessary to achieve bioequivalence to the reference product (Bird and Ravindra 2020). Thus, the test formulation delivers the same nominal dose through a smaller patch area, consisting of a more compact transdermal system, without compromising systemic exposure.

The clinical studies for the 6.84 mg (nominal delivered dose 4.6 mg/24 h) and 20.52 mg (nominal delivered dose 13.3 mg/24 h) were waived based on the identical release mechanism, same manufacturing site, formulation proportionality similarity (excipients and dimensions), and comparable *in vitro* release profiles with the bio-batch of 13.68 mg (nominal delivered dose 9.5 mg/24 h) (ANVISA 2022).

2.4. Drug Administration

The reference product's prescribing information recommends applying the rivastigmine transdermal patch once daily to clean, dry, hairless and intact skin on the upper or lower back, upper arm, or chest, avoiding areas that may be subjected to friction from tight clothing (United Medical LTDA.). To standardize administration and minimize mechanical interference, the patch was applied to the deltoid region of either the right or left upper arm, with the side allocated according to the randomization schedule, ensuring that a site previously exposed or potentially irritated at the first study period was not reused in the subsequent period.

Throughout each study period, volunteers remained in the clinical facilities for 48 hours. To preserve the integrity of adhesion performance assessment, specific measures were adopted to minimize any unintended patch detachment during the wearing period. Bathing routines were standardized by not allowing showers between 3 hours before and 24 hours after patch application. Such precaution aimed to limit external interference with the patch and thereby reduce potential bias in the evaluation of adhesion performance.

Approximately 1 hour before dosing, the selected area was gently washed with a moistened pad (water only) and carefully dried without rubbing, to avoid skin irritation. The application site had to be clean, dry, hairless, and free from powders, oils, moisturizers, lotions, tattoos, vitiligo, scars, or any cutaneous lesions that could compromise patch adhesion. Participants were instructed not to wear clothing with seams or tight folds over the patch, not to lie on the application site, and not to touch, scratch, or press the transdermal system with their hands. Patch application and removal were always performed by trained staff using disposable gloves to minimize manipulation and ensure consistent adhesion throughout the dosing interval.

In each study period, participants underwent an overnight fast of at least 8 hours. Following patch application, they remained without food for an additional 4 hours and were instructed to restrict fluid intake during the 2 hours before and after dosing. The type and schedule of meals and beverages were kept uniform for all volunteers in both periods to minimize dietary variability. In addition, alcohol or any products containing caffeine or other xanthine were not allowed during the 48 hours preceding study participation.

2.5. Sampling and Bioanalysis

For bioanalytical purposes, a total of 21 venous blood samples were collected in each study period at the following scheduled time points: before dosing (0.00 h) and at 2.00, 3.00, 6.00, 7.00, 8.00, 9.00, 10.0, 11.0, 12.0, 13.0, 14.0, 15.0, 16.0, 18.0, 20.0, 24.0, 28.0, 32.0, 36.0, and 48.0 hours following transdermal patch application. Blood samples were collected into heparin-containing tubes and centrifuged at 3,000 rpm for 5 min at 4°C. Plasma was subsequently separated, transferred to properly identified cryovials, and stored at – 80°C until bioanalysis.

Rivastigmine plasma concentrations were determined using a fully validated high-performance liquid chromatography coupled with tandem mass spectrometry (HPLC–MS/MS) method. The analytical platform comprised an Agilent 1200 Series liquid chromatograph interfaced with an API 6500 triple quadrupole mass spectrometer (Sciex, Framingham, MA, USA). Sample preparation was performed by protein precipitation, with donepezil hydrochloride (USP, Rockville, MD, USA) employed as the internal standard. To minimize analytical variability, all samples obtained from each participant were analyzed within the same batch.

Chromatographic analysis was carried out using a 12 µL injection volume onto an ACE Generix 5 C18 column (4.6 × 100 mm, 5 µm; Avantor Inc., Great Britain, UK), maintained at 30°C. Isocratic elution was performed at a flow rate of 1 mL/min using a mobile phase consisting of acetonitrile:methanol (1:1) and 2 mM ammonium formate in a 60:40 (v/v) ratio. Detection was achieved by positive electrospray ionization in multiple reaction monitoring (ESI+/MRM) mode, with mass transitions of m/z 251.200 → 206.000 for rivastigmine and m/z 380.300 → 91.000 for the internal standard.

Quantification was based on calibration curves constructed over a concentration range of 30 to 15,000 pg/mL. The bioanalytical method was validated in compliance with the Brazilian regulatory authority (ANVISA) guidelines (ANVISA 2012), encompassing evaluations of selectivity, potential interference from co-administered drugs, matrix effects, carryover, calibration model performance, intra- and inter-run precision and accuracy, reinjection reproducibility and analyte stability under different storage and processing conditions.

2.6. Pharmacokinetic and Bioequivalence Assessment

Pharmacokinetic metrics were subjected to statistical evaluation for bioequivalence assessment using Phoenix WinNonlin™ software (version 6.4; Princeton, NJ, USA). The extent of systemic exposure up to

the last measurable concentration (AUC_{0-t}) was estimated by non-compartmental analysis employing the linear trapezoidal approach.

Total exposure extrapolated to infinity (AUC_{0-inf}) was obtained by summing AUC_{0-t} to the extrapolated terminal area (C_n/k_{el}), calculated as the ratio between the last quantifiable concentration (C_n) and the terminal elimination rate constant (k_{el}). The value of k_{el} was estimated from the terminal log-linear portion of the plasma concentration–time profile. Elimination half-life ($t_{1/2}$) was subsequently calculated as $\ln 2/k_{el}$. Peak systemic concentration (C_{max}) and the corresponding time to peak (t_{max}) were directly determined from the observed data without interpolation.

In accordance with the regulatory framework established by ANVISA for bioequivalence studies involving TDDS, two partial areas under the concentration–time profile (pAUCs), intended to capture distinct phases of drug absorption and disposition, were defined as primary endpoints alongside conventional parameters (C_{max} and AUC_{0-t}). These included: (i) an early pAUC, corresponding to the area from dosing to the midpoint of the dosing interval (from 0 to 12 h); and (ii) a terminal pAUC, representing the area from the midpoint of the dosing interval to the last quantifiable concentration (from 12 to 48 h).

Bioequivalence was evaluated by constructing 90% confidence intervals (90%CI) for the geometric mean ratios (GMR) between the test and reference formulations for log-transformed C_{max} and exposure metrics (AUC_{0-t} and pAUCs). The bioequivalence was concluded if these intervals fell within the predefined acceptance range of 80.00–125.00%. A mixed-effects analysis of variance (ANOVA) model was applied to assess the influence of sequence, period, and treatment, which were included as fixed effects in the statistical model.

2.7. Adhesion Performance

Adhesion assessments were performed according to the crossover design of the study. The adhesive performance of the rivastigmine TDDSs was evaluated at predefined intervals, namely immediately after application (time zero) and at 4:00, 8:00, 12:00, 16:00, 20:00, and 24:00 h post-application. Adhesion was quantified by determining the proportion of the patch surface remaining in contact with the skin over time. For this purpose, custom-designed templates made from transparent polymeric material were gently positioned over the applied patches to enable visualization and delineation of areas exhibiting partial or complete detachment.

Owing to differences in geometry and surface area between the test and reference products (7.8 cm² and 10 cm², respectively), distinct templates were employed for each formulation (Fig. 2). The templates were internally subdivided into concentric and radial segments specifically designed to generate regions with comparable surface areas. This standardized segmentation strategy enabled a more accurate identification and quantification of partially or fully detached areas, ensuring that each predefined region contributed equally to the overall adhesion assessment and reducing potential bias associated with heterogeneous area distribution.

The extent of adhesion was expressed as the percentage of the patch surface still adhered to the skin, calculated by subtracting the sum of detached areas from the total nominal area. Adhesive performance at the end of the dosing interval (24 h) was defined as the primary endpoint for comparative analysis.

In accordance with the EMA guideline (European Medicines Agency (EMA).), adhesion equivalence or non-inferiority was assessed using a tiered decision framework. When the reference product demonstrated a high degree of adhesion (defined as $\geq 90\%$), the test formulation was considered equivalent if the lower bound of the two-sided 90% confidence interval (CI) for its mean percentage of adhesion at 24 h exceeded 90%. Conversely, when the reference formulation exhibited low adhesive performance ($< 90\%$), non-inferiority of the test product was concluded if the lower bound of the 90% CI for the difference in adhesion between test and reference formulations (expressed as a continuous variable) was greater than the predefined non-inferiority margin. As per EMA recommendations, for statistical evaluation, this margin ($-\delta$) was established at -10% (EMA 2014).

2.8. Safety

Safety evaluations were based on repeated assessments of vital parameters, including body temperature, arterial blood pressure, heart rate, and respiratory rate, obtained at baseline and at scheduled intervals during the trial. In addition, comprehensive laboratory investigations—comprising hematological analyses, urinalysis, and serum biochemistry—along with physical examinations and 12-lead electrocardiograms (ECGs), were performed at both study entry and study completion. The study participants were kept under continuous clinical surveillance throughout all study phases.

The occurrence of adverse events was systematically monitored by qualified nursing and medical personnel during the entire confinement period. Participants were explicitly instructed to promptly communicate any unexpected symptoms, discomfort, or health-related alteration experienced either during the study procedures or following discharge. Reported adverse events were categorized according to intensity (mild, moderate, or severe), and their potential relationship to the investigational product was evaluated by the medical team and classified as either related or unrelated.

3. Results

3.1. Study Population

Of the 74 participants enrolled, 68 healthy participants were selected for the study, and 58 (29 men and 29 women) completed the two periods, being included in the pharmacokinetic and adhesion evaluation, and statistical analysis. Table 2 shows the demographic characteristics of the participants who completed all phases of the study.

Table 2
Demographic characteristics of the study subjects.

Age (years)	Descriptive statistics (n = 58)
Mean ($\pm$ SD)	33.24 ($\pm$ 8.13)
Range	18–47
Weight (kg)	
Mean ($\pm$ SD)	70.75 ($\pm$ 10.06)
Range	52.5–98.7
Height (m)	
Mean ($\pm$ SD)	1.68 ($\pm$ 0.09)
Range	1.49 – 1.92
BMI (kg/m ²)	
Mean ($\pm$ SD)	24.90 ($\pm$ 2.56)
Range	19.23–29.91
Gender (n [%])	
Male	29 (50%)
Female	29 (50%)

During the first study period, following drug administration, one participant was excluded due to an episode of vomiting, and one participant was withdrawn owing to a local reaction at the application site. In addition, one participant was discontinued from the study because of the occurrence of respiratory symptoms. In the second study period and prior to drug administration, three participants were excluded because of the use of concomitant medications not permitted by the study protocol. Furthermore, two participants were withdrawn due to respiratory symptoms and positive diagnostic test for COVID-19, respectively; one participant was excluded due to an episode of diarrhea occurring before hospitalization, and one participant was discontinued for personal reasons.

3.2. Pharmacokinetic Analysis

Figure 3 depicts the average plasma concentration–time profiles derived from the 58 participants who completed both study periods. The distribution of blood sampling points allowed for an adequate characterization of the drug absorption process during the dosing interval (0–24 h), as well as a reliable assessment of the elimination phase following patch removal.

The main pharmacokinetic parameters obtained for rivastigmine following administration of the test and reference formulations are summarized in Table 3. In addition to conventional exposure metrics, pAUCs were determined to comply with ANVISA regulatory criteria applicable to bioequivalence assessments of TDDS. Specifically, AUC_{0-12} and AUC_{12-48} were calculated to allow evaluation of formulation comparability across distinct phases of the dosing interval, thereby supporting the assessment of equivalence throughout the entire exposure period.

Table 3

Pharmacokinetic metrics of rivastigmine for the test (Rivastigmine Transdermal Patches – 13.68, 9.5 mg/24h mg) and the reference (Exelon® Patch 10, 18 mg 9.5mg/24h) patch formulations administered in healthy subjects (N = 58). Data expressed as mean (± SD).

Parameter	Test	Reference
C_{max} , pg/mL	6,563 (± 3,3565)	6,562 (± 3,620)
AUC_{0-t} , pg/mL·h	105,754 (± 51,735)	108,052 (± 56,168)
AUC_{0-12} , pg/mL·h	29,702 (± 23,233)	30,476 (± 24,456)
AUC_{12-t} , pg/mL·h	76,052 (± 31,889)	77,576 (± 34,582)
AUC_{0-inf} , pg/mL·h	108467 (± 51,751)	110,869 (± 60,335)
t_{max} , h	14.5 (± 3.7)	14.4 (± 3.7)
$t_{1/2}$, h	4.7 (± 3.4)	4.7 (± 2.4)
C_{max} , maximum plasma concentration; AUC_{0-t} , area under the concentration-time curve from zero to 48 h; AUC_{0-inf} , area under the concentration-time curve extrapolated to infinity; AUC_{0-12} , area under the concentration-time curve from zero to 12 h; AUC_{12-t} , area under the concentration-time curve from 12 to 48 h; t_{max} , time to C_{max} ; $t_{1/2}$, elimination half-life.		

3.3. Bioequivalence Assessment

Among the participants included in the pharmacokinetic evaluation, two had pre-dose plasma concentrations greater than 5% of their respective C_{max} in the corresponding study period. In accordance with the Brazilian regulatory guideline these data were excluded from the primary bioequivalence analysis (ANVISA 2022). To assess the robustness of the bioequivalence conclusions, a complementary analysis was carried out including all participants who completed the clinical phase, and the bioequivalence conclusions remained unchanged (data not shown).

Table 4 presents the estimated GMR between the test and reference formulations for key pharmacokinetic parameters, including C_{max} , AUC_{0-t} , AUC_{0-inf} , AUC_{0-12} , and AUC_{12-t} , together with their respective 90% confidence intervals, within-subject coefficients of variation (CV_{ws}), and the associated statistical power (TOST) of the bioequivalence assessment.

Table 4
Geometric mean ratio, confidence intervals (90%), CV_{ws} , and power (N = 56).

Parameter*	GMR (%)	90% CI	CV_{ws} (%)	Power (%)
C_{max}	100.78	92.83–109.41	26.37	99.50
AUC_{0-t}	98.35	92.24–104.86	20.43	99.99
AUC_{0-12}	97.84	88.82–107.78	31.24	95.79
AUC_{12-t}	98.43	92.72–104.49	19.01	100.00
AUC_{0-inf}	99.32	92.05–107.15	24.30	99.85
*Parameters logarithmically transformed; GMR, geometric mean ratio; CI, 90% confidence interval; CV_{ws} , within-subject coefficient of variation.				

As all 90% confidence intervals for the GMR between the test and reference formulations fell within the predefined bioequivalence limits of 80.00–125.00% established by ANVISA, both rivastigmine TDDS systems demonstrated to be bioequivalent with respect to both the rate and extent of absorption. Across all evaluated pharmacokinetic parameters, no significant differences were identified for the sequence effect (at 10% significance level) or for treatment effect (at 5% significance level). A statistically significant period effect ($p < 0.05$) was observed for C_{max} , AUC_{12-t} , and AUC_{0-inf} parameters; however, this finding was considered not clinically meaningful.

3.4. Adhesion Performance

Figure 4 illustrates the adhesion performance of each TDDS formulation throughout the dosing period (24 h), considering all participants who completed the study. The graphical representation allows visualization of the temporal evolution of adhesive performance within the dosing interval.

At the end of the dosing period (24 hours), the reference product exhibited an adhesion performance level below 90%, so the non-inferiority analytical criterium was applied for the statistical comparison between test and reference formulations. These analysis outcomes and the predefined non-inferiority margin are summarized in Table 5.

Table 5
Non-inferiority *analysis* for the mean percentage of adhesion at the end of the dosing interval (24 hours after patch application) comparing the test and the reference formulations (N = 58).

Reference	Mean (%)	SE (%)	90% CI
	79.97	2.39	76.00–83.95
Test	77.53	2.39	73.56–81.50
Difference (T – R)	-2.44	2.87	-7.24–2.36
Non-inferiority margin (- δ)	- 10%	--	--
Statistical Power	100%	--	--
Ratio (T/R)	96.95	--	90.94–102.95
SE: standard error; 90% CI: confidence interval of 90%			

The non-inferiority in adhesion was demonstrated for test formulation since the mean difference between formulations was estimated at - 2.44% and the lower limit of the 90% CI for this difference was estimated at -7.24%, greater than the non-inferiority margin established for the analysis (-10%).

3.5. Safety

Of the 74 subjects enrolled in the study, 42 participants reported a total of 92 adverse events. All events were classified as non-serious and mild in intensity. Regarding causality, 61 events were considered related (likely) to the study medication, while 31 were considered unrelated (unlikely). Table 6 describes the reported events with an incidence $\geq 2\%$. Both test and reference products were well tolerated.

Table 6
Incidence of adverse events reported (N = 74 subjects; 92 adverse events).

Adverse Event	Incidence N (%)	Causality	Intensity
Headache	23 (25%)	Related	Mild
Leukocyturia	14 (15.2%)	Related	Mild
Nausea	11 (12%)	Related	Mild
Hematuria/Hemoglobinuria	11 (12%)	Unrelated	Mild
Dizziness	6 (6.5%)	Related	Mild
Vomiting	4 (4.3%)	Related	Mild
Increased Transaminases	3 (3.3%)	Unrelated	Mild
Coryza/Sneezing	2 (2.2%)	Unrelated	Mild
Dysmenorrhea	2 (2.2%)	Unrelated	Mild
Hyperglycemia	2 (2.2%)	Unrelated	Mild
Hypertriglyceridemia	2 (2.2%)	Unrelated	Mild
Others	10 (< 2%)	--	--

4. Discussion

4.1. Pharmacokinetic and Bioequivalence Assessment

The present study demonstrated bioequivalence between the test formulation of rivastigmine TDDS (Rivastigmine Transdermal Patches – 13.68 mg – 9.5 mg/24 h) and the reference formulation (Exelon[®] Patch 10, 18 mg – 9.5 mg/24 h) following single-dose administration in healthy volunteers. The 90% CIs for GMRs of the primary pharmacokinetic parameters (C_{max} , AUC_{0-t} , AUC_{0-12} , AUC_{12-t}) fell within the acceptance limits of 80.00–125.00% as required by ANVISA (ANVISA 2022), confirming the bioequivalence between the test product and the reference transdermal patch marketed in Brazil.

The pharmacokinetic profile observed for both formulations was characterized by a slow and sustained absorption, with a mean t_{max} of 14.00 hours. This value is consistent with historical data for rivastigmine patches (Exelon[®] Patch), for which the t_{max} reported in healthy volunteers typically ranges between 10 and 16 hours, depending on the application site (United Medical LTDA.). Lefèvre et al. (Lefèvre et al. 2007) observed a mean t_{max} of 16 hours for applications on the upper back or upper arm sites corroborating the appropriateness of the methodology employed in this study. The absence of abrupt concentration spikes reflects the controlled-release kinetics typical of the transdermal route, which aims

to minimize the peak-to-trough fluctuations often associated with the gastrointestinal adverse effects of oral cholinesterase inhibitor formulations (Kurz et al. 2009).

With respect to pharmacokinetic parameters, the findings of the present study are consistent with those reported in the CHMP Assessment Report issued by EMA for Rivastigmine Actavis transdermal patches product (EMA 2013). According to that report, the reference product (9.5 mg/24 h) exhibited a mean $C_{\max}$ of 8,026 pg/mL, a mean AUC_{0-t} of 134,414 pg/mL·h, and a mean AUC_{0-inf} of 136,142 pg/mL·h, values that are in close agreement with those obtained in the present study, as summarized in Table 3.

In addition, the pharmacokinetic outcomes observed in the present investigation are consistent with those reported in Study 2332 for the Exelon Patch (reference product) included in the FDA Clinical Pharmacology and Biopharmaceutics Review (FDA 2007). In that evaluation, administration of the reference formulation (9.5 mg/24 h) resulted in a mean $C_{\max}$ of 5.8 ng/mL and a mean AUC_{0-inf} of 118 ng/mL·h, which are comparable to the exposure levels determined in this study.

The CV_{ws} observed in this study were moderate, ranging from 19.01% for AUC_{12-t} to 31.24% for AUC_{0-12} . The CV_{ws} for $C_{\max}$ and AUC_{0-t} were approximately 26% and 20%, respectively. These values align favorably with the literature; Morte et al. (Morte et al. 2022) reported within-subject variability in the 30–35% range in multiple-dose bioequivalence studies of 13.3 mg/24 h patches. Additionally, the statistical power calculated for all parameters exceeded 95%, indicating that the sample size was sufficiently robust to detect differences between the formulations.

It is important to note that bioequivalence was established not only for the total extent of absorption AUC_{0-t} but also for the absorption rate and the release profile over time. The equivalence in pAUC suggests that the test formulation attains a similar pattern of drug flux through the skin with respect to the reference product, maintaining constant and equivalent therapeutic delivery until patch removal. To the best of our knowledge, this is one of the first published studies demonstrating the utility of partial AUCs as primary endpoints for bioequivalence assessment between two formulations of rivastigmine transdermal patch.

Previous studies, such as Schurad et al. (Schurad et al. 2022), have highlighted the importance of consistent systemic exposure for maintaining butyrylcholinesterase inhibition and clinical efficacy. The similarity in the concentration-time curves obtained (Fig. 1) reinforces that switching between formulations should not result in alterations in pharmacodynamic response or safety. Such comparative analyses are essential to confirm the equivalence of the formulations, the adequacy of the study design and their ability to reliably characterize the pharmacokinetic profile of rivastigmine following administration using a TDDS.

4.2. Adhesion Performance

At the end of the dosing interval (24 h), the skin adhesion was comparatively evaluated for both test and reference rivastigmine TDDS. The adhesion profiles (Fig. 2) indicate that the test formulation maintained

comparable adhesion throughout the dosing period relative to the reference product. The statistical approach was defined in accordance with the EMA guideline (EMA 2014) using the adhesion performance of the reference formulation as the benchmark. Given that the reference product exhibited a mean adhesion performance below 90% at the end of the dosing interval, a non-inferiority analysis was applied to compare both formulations.

As summarized in Table 4, the mean difference between treatments was – 2.44%, with the lower bound of the corresponding confidence interval calculated as -7.24%, greater than the pre-specified non-inferiority margin of – 10%.

A distinct feature of the test formulation is its reduced area compared to the reference product. Typically, larger patches are more susceptible to mechanical stress and edge lifting caused by skin movement and friction against clothing (Wokovich et al. 2006; FDA 2021). By achieving the same therapeutic delivery rate (9.5 mg/24 h) with a smaller footprint, the test product may offer potential advantages regarding patient comfort and reduced local impact during daily wear.

It should also be noted that adhesion assessments were conducted using a within-subject design, in which both formulations were applied to the same participants in different study periods on contralateral application sites. This methodological approach minimized the impact of inter-individual variability associated with skin properties, reinforcing the reliability of comparative findings (FDA 2021; Davanço et al. 2024).

4.3. Safety

Across the 74 participants enrolled in the study, a total of 92 adverse events were documented following administration of both the test and reference transdermal formulations. The most frequently reported events were headache (25%), leukocyturia (15.2%), nausea (12%), and hematuria/hemoglobinuria (12%). Notably, headache and nausea are classified as common and very common adverse reactions, respectively, in the approved labeling of the rivastigmine TDDS (United Medical LTDA.). In contrast, leukocyturia and hematuria/hemoglobinuria are not established as common adverse drug reactions associated with rivastigmine therapy. These findings were predominantly mild, transient, and assessed as not related to the investigational product. No temporal pattern consistent with a drug-related mechanism was observed, and no participant required discontinuation due to urinary abnormalities. More than that, no serious adverse events were observed throughout the trial.

Importantly, gastrointestinal (GI) events – which represent a major tolerability limitation of orally administered cholinesterase inhibitors – were observed at relatively low frequency. Nausea occurred in 12% of participants, whereas vomiting and diarrhea were even less frequent (> 5%). This finding is clinically relevant, as GI intolerance is a well-recognized dose-limiting factor for oral rivastigmine therapy. In pivotal comparative trials, oral rivastigmine capsules were associated with substantially higher incidences of nausea (23%) and vomiting (17%), frequently leading to treatment discontinuation. In contrast, the transdermal patch demonstrated significantly lower rates of GI adverse reactions, attributed

to its ability to provide continuous drug delivery and reduced peak plasma concentrations ($C_{\max}$), thereby minimizing cholinergic overstimulation of the gastrointestinal tract (Winblad et al. 2007a).

Collectively, these findings confirm that both transdermal formulations were well tolerated and aligned with the established safety of rivastigmine patches therapy. The low incidence of clinically significant gastrointestinal events further reinforces the therapeutic rationale for transdermal administration as a strategy to enhance tolerability relative to oral cholinesterase inhibitors. Importantly, although this was a single-dose study, the observed safety profile was favorable, with exclusively mild adverse events and no serious occurrences. While longer exposure is required to fully characterize cumulative tolerability, the absence of clinically meaningful safety signals following acute administration provides supportive evidence of the short-term safety and comparability of the test and reference formulations.

5. Conclusions

The comprehensive evaluation presented in this report confirms the bioequivalence, non-inferiority in adhesion, and systemic tolerability of the new transdermal patch relative to the reference product available on the Brazilian market. The demonstration of bioequivalence, coupled with comparable adhesion and safety profiles, supports the therapeutic interchangeability of the test formulation.

In accordance with the FDA product-specific guidance for rivastigmine TDDS (FDA 2019), demonstration of bioequivalence and adequate adhesion must be complemented by an assessment of dermal irritation and sensitization to ensure the safety of generic products. Accordingly, the test formulation was evaluated against the reference in a separate clinical investigation (data not shown), in which comparable safety was confirmed with respect to skin irritation and sensitization outcomes.

A limitation of the present investigation is that it was conducted exclusively in healthy volunteers. Therefore, interpretation of the safety findings derived from this bioequivalence study should be approached with caution, given that the evaluation was based on single-dose administration under controlled conditions. Ongoing pharmacovigilance activities and structured post-marketing surveillance programs remain essential to monitor and identify potential safety signals during routine clinical use.

Overall, considering the similarity in bioavailability, patch adhesion behavior, and safety outcomes, Rivazich[®], the rivastigmine patches formulation marketed in Brazil by Adium S.A. shall be considered therapeutically equivalent to the reference product (Exelon[®] Patch 10). Consequently, both products provide equivalent clinical efficacy and may be regarded as interchangeable in medical practice.

Abbreviations

The following abbreviations are used in this manuscript:

AD	Alzheimer's disease
ACh	Acetylcholine
GI	Gastrointestinal
$C_{\max}$	Peak plasma concentration
$t_{\max}$	Time to peak concentration
TDDS	Transdermal drug delivery system
ICH	International Council for Harmonization
ANVISA	Brazilian Health Regulatory Agency
BMI	Body mass index
CV_{ws}	Whitin-subject coefficient of variation
EMA	European Medicines Agency
PAA	Patch Area Activity
HPLC-MS/MS	High-performance liquid chromatography coupled with tandem mass spectrometry
ESI-MRM	Electrospray ionization in multiple reaction monitoring
k_{el}	Terminal elimination rate constant
$t_{1/2}$	Elimination half-life
90%CI	90% confidence interval
AUC_{0-t}	Area under the curve from zero to last measurable concentration
AUC_{0-inf}	Area under the curve extrapolated to infinity
AUC_{0-12}	Partial AUC from zero to 12 hours
AUC_{12-t}	Partial AUC from 12 hours to last measurable concentration
pAUC	Partial area under the curve
GMR	Geometric mean ratio
CI	Confidence interval
CV_{ws}	Within-subject coefficient of variation
TOST	Two one-sided t-tests
ANOVA	Analysis of variance
SD	Standard deviation

SE	Standard error
ECG	Electrocardiogram
COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
RT-qPCR	Quantitative reverse transcription polymerase chain reaction

Declarations

Ethics approval and consent to participate:

The study was conducted in accordance with the Declaration of Helsinki and approved by Research Ethics Committee of the Instituto de Ciências Farmacêuticas de Estudos e Pesquisas (Goiânia, GO, Brazil), protocol number 5.999.355, approved on April 13rd, 2023. An informed consent was obtained from all subjects involved in the study.

Consent for publication:

Not applicable. This study does not include any identifiable individual data.

Competing Interests

The authors M.F., A.S., L.S.T., K.B.B. and A.C.C.S. declare no conflict of interest regarding the publication of this article. T.M.d.S, D.R.B.V., J.M., and C.F.P.V are employees of Adium S.A (sponsor of the study). F.C. is an employee of Adium Pharma S.A., a company from Adium group. The authors were fully responsible for all content and editorial decisions.

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Author Contribution

Conceptualization, M.F., A.S., K. B.B., F. C. and C.F.P.V.; Data curation, T. M.S., J. M., D.R.B.V., K.B.B, A.C.C. and C.F.P.V.; Investigation, K.B.B and A.C.C.; Methodology, M. F., A.S., K.B.B and C.F.P.V.; Project Administration, C.F.P.V.; Software, T.M.S, K.B.B and A.C.C.; Supervision, L.S.T, F.C. and C.F.P.V.; Validation, K.B.B., A.C.C, L.S.T and C.F.P.V.; Writing – original draft, T.M.S; Writing – review & editing, J.M., D.R.B.V., M.F., A.S., F.C. and C.F.P.V.

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Data Availability

The datasets generated and/or analyzed during the current study are not publicly available due to ethical, privacy, and regulatory restrictions related to the protection of study participants.

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Figures

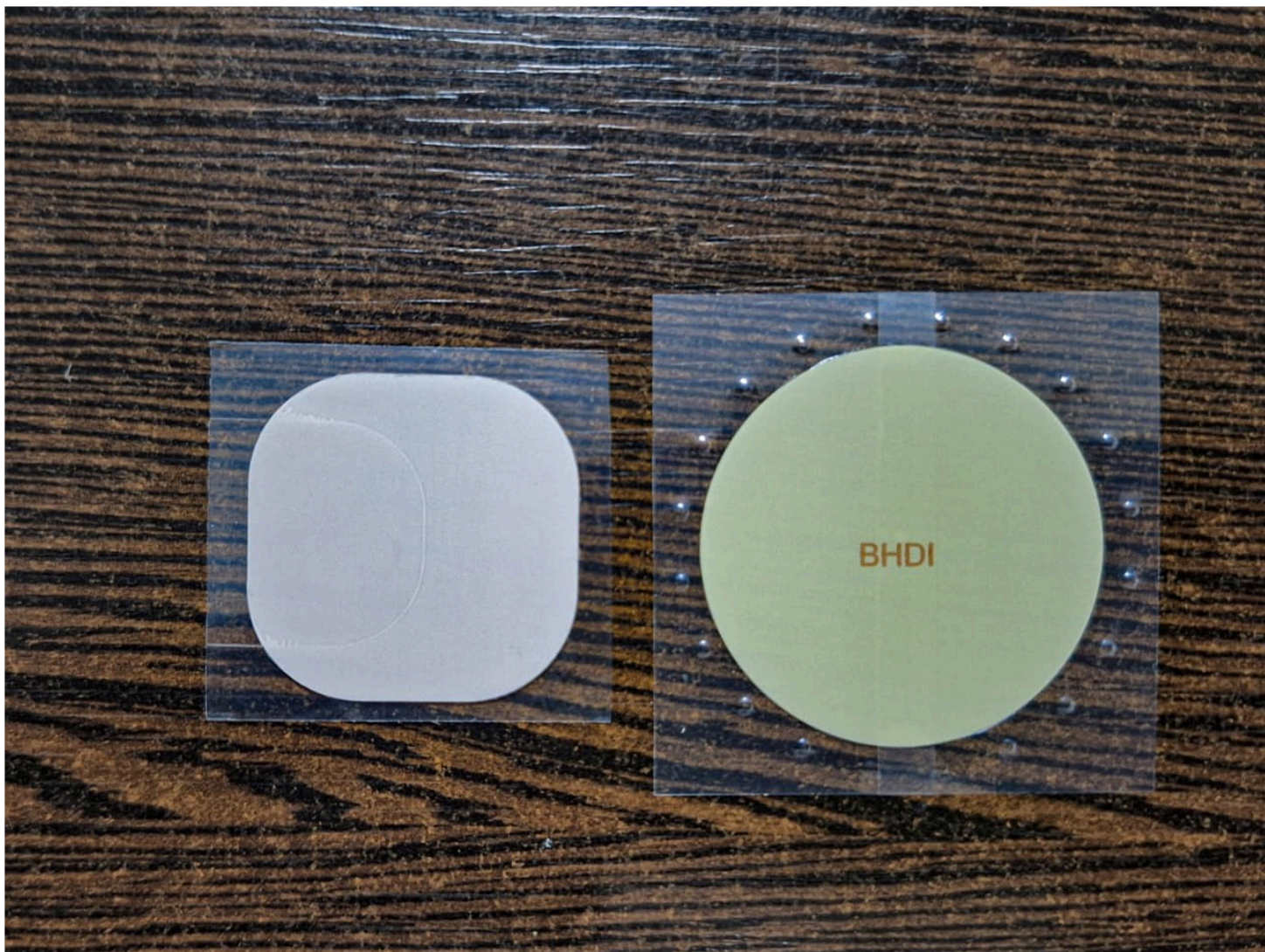


Figure 1

Photograph of the test (left) and reference (right) formulations used in the study.

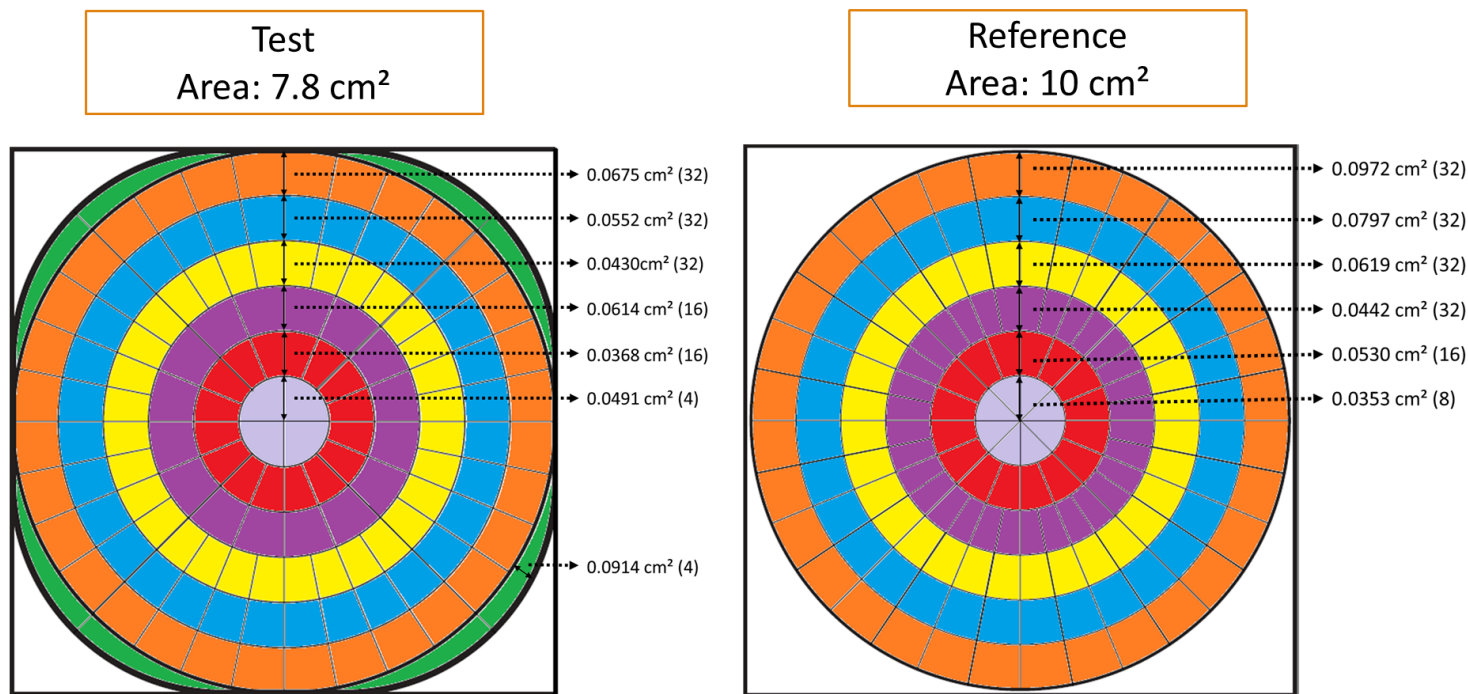


Figure 2

Representative schematic of the custom-designed transparent templates used for adhesion assessment of the test (7.8 cm²) and reference (10 cm²) rivastigmine patches. The templates were subdivided into color-coded concentric rings and radial sectors of comparable area. Arrows indicate the area of each sector, and the total number of sectors within each annular region is indicated in brackets.

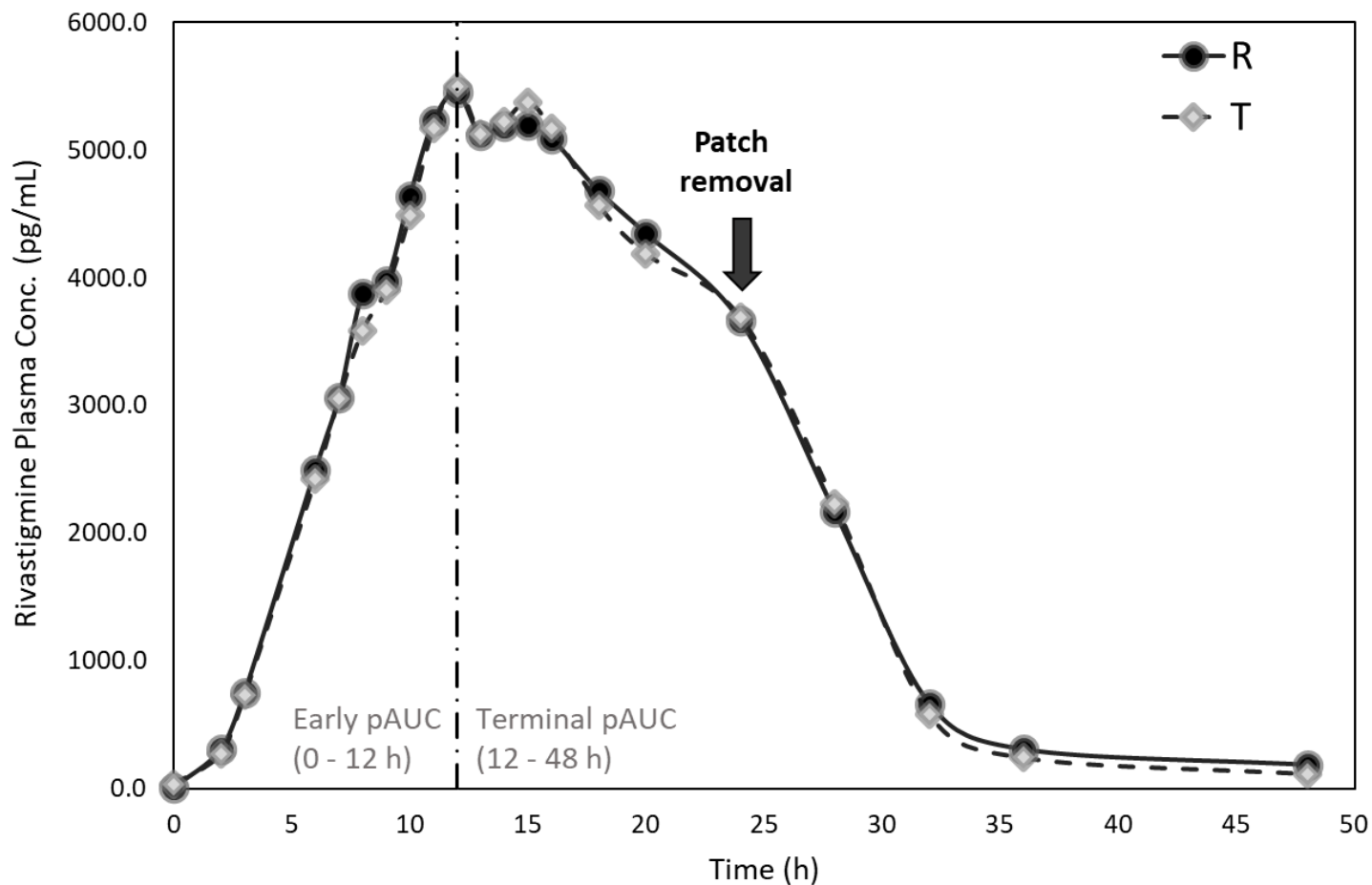


Figure 3

Mean plasma concentration-time profile after administration of the rivastigmine test (T) and the reference (R) patch formulations in healthy subjects (N=58). The patches were removed 24 h after the application, and the blood samples were collected up to 48 h. pAUC: partial area under the curve.

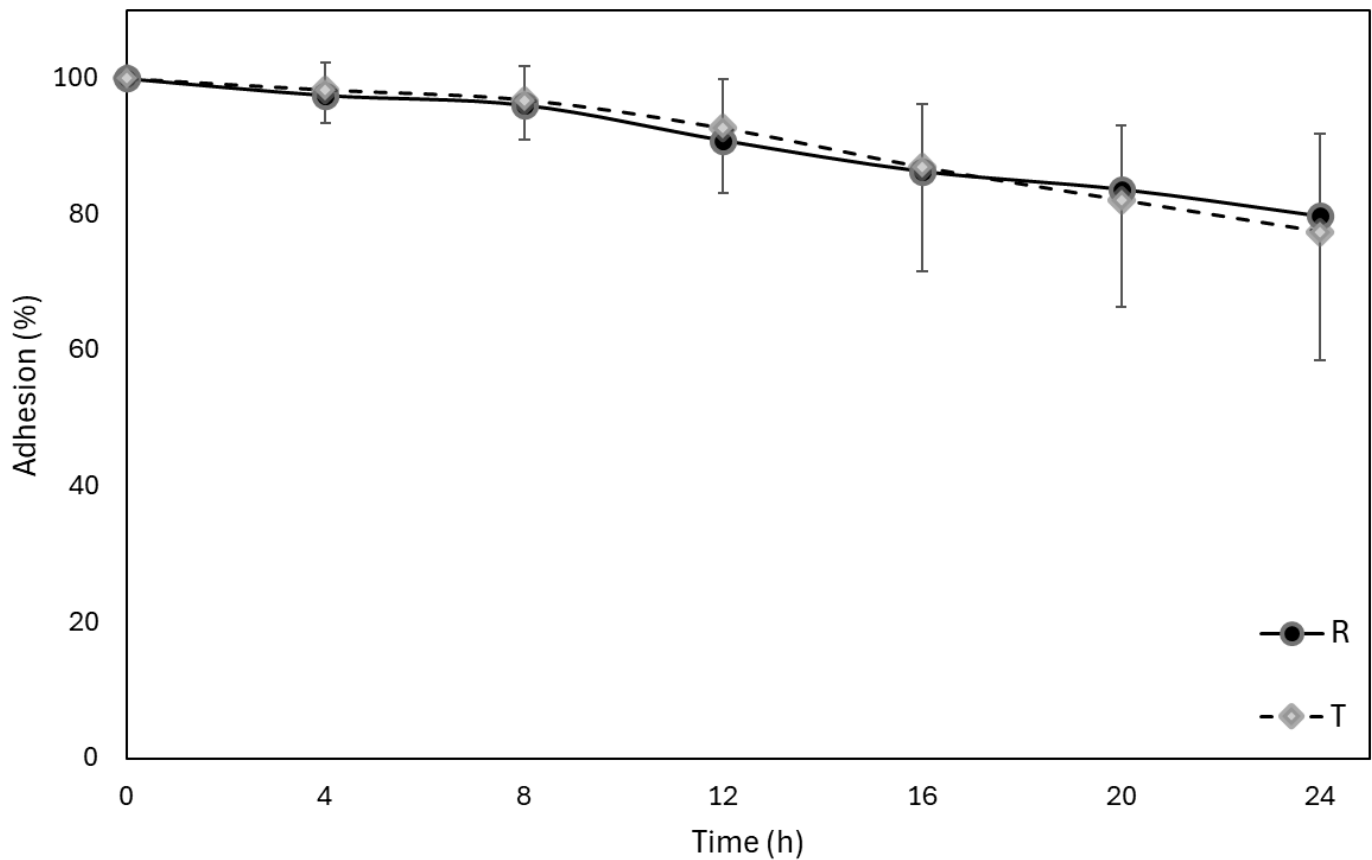


Figure 4

Rivastigmine TDDS adhesion performance within the dosing interval (24 hours) for the test (T – Rivastigmine Patches – 13.68 mg, 9.5mg/24 h) and reference (R - Exelon[®] Patch 10 – 18 mg, 9.5 mg/24 h) patch formulations. Data are expressed as mean $\pm$ SD (N = 58).

Supplementary Files

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