Rev Soc Esp Dolor
2017; 24(2):59-67

DOI: 10.20986/resed.2017.3565/2017

Paxiflas®: new FDT combination of tramadol/paracetamol for treating moderate to severe pain

C. Tornero-Tornero[1], J. Galván[2], I. García[2], M. Boyer[3] and J. Orduña Valls[1]

[1]Unidad Dolor. Servicio de Anestesiología. Hospital Clínico Universitario. Valencia. [2]Departamento Médico. Laboratorios Gebro Pharma S.A. [3]Departamento Clínico. Athena Drug Delivery

Tornero-Tornero C, Galván J, García I, Boyer M y Orduña Valls J. Paxiflas®: new FDT combination of tramadol/paracetamol for treating moderate to severe pain. Rev Soc Esp Dolor 2017;24(2):59-67.

ABSTRACT

Introduction: Paxiflas® is the combination of tramadol hydrochloride/paracetamol (37.5/325 mg) in mentholated, fast disintegrating tablets (FDTs), marketed by Laboratorios Gebro Pharma S.A. FDTs dissolve rapidly in the mouth without the need for water. They are intended for active patients who do not have access to drinking water at all times, busy individuals, or people who travel frequently. Moreover, they are especially indicated for individuals with difficulties in swallowing,the elderly and help to improve therapeutic compliance. In addition, it combines the rapid action of paracetamol with the longer action of tramadol hydrochloride.

Objectives: To demonstrate the bioequivalence between Paxiflas® FDTs administered with or without water, and tablets of the reference product, Zaldiar®, administered with water, in healthy subjects on an empty stomach.

Material and methods: Open-label, balanced, randomized, crossover, single-oral-dose study, of 3 treatments in 3 periods and 3 sequences, with a washout period of 7 days between periods I and II, and 8 days between periods II and III. Volunteers were randomized to receive a single oral dose (2 tablets) of Paxiflas®, administered without water (product A) or with water (product B), and Zaldiar® with water. Bioequivalence was considered met if the 90 % confidence interval (90 % CI) of geometric mean ratio of C_{max} and AUC_{0-t} between test and reference product fell within the range of 80-125 % for (+) tramadol, (-) tramadol, and paracetamol. The secondary objective was to monitor the safety and tolerability of products A and B.

Results: Bioequivalence was evaluated in 38 subjects for product A and in 39 subjects for product B. Peak plasma concentration levels of (+) tramadol were achieved at 0.75-3 h for product A, at 0.5-4 h for product B, and at 0.5-3 h for the reference product. In the case of (-) tramadol, plasma levels were reached at 0.75-3 h for product A, at 0.5-4 h for product B, and at 0.5-3 h for reference product. Finally, plasma levels of paracetamol were achieved at 0.25-2.5 h for product A, at 0.5-2 h for product B, and at 0.25-2.5 h for the reference product. Bioequivalence (90 % CI, lying within the acceptable range of 80.00-125.00 %) was met in 38 subjects receiving product A and 39 subjects receiving product B. Tramadol HCl/paracetamol FDTs were well-tolerated. A total of 6 adverse events (AEs) were reported during the study (headache, giddiness, abdominal pain, itching on forearms and thighs, and increased eosinophil count), of which 3 were expected and possibly related to the study product. The AEs were mild to moderate in severity. No serious AE was observed during the study.

Discussion: Data from this study demonstrate bioequivalence between Paxiflas® FDTs, administered with and without water in different periods, and tablets of Zaldiar®, administered with water, in terms of rate and extent of absorption on an empty stomach.

Key words: Bioequivalence, tramadol, paracetamol, fast disintegrating tablets, pain, treatment.

Received: 18-01-17.
Accepted: 19-01-17.

Correspondence: Carlos Tornero Tornero
carlostornero@gmail.com

RESUMEN

Introducción: Paxiflas® es la combinación de clorhidrato de tramadol/paracetamol (37,5 mg/325 mg) en forma de comprimidos bucodispersables de sabor mentolado, comercializado por Laboratorios Gebro Pharma S.A. Los comprimidos bucodispersables se dispersan rápidamente en la boca sin necesidad de agua. Están destinados a pacientes activos que no dispongan de agua en todo momento, personas ocupadas o que viajen con asiduidad. Además, son adecuados en personas con problemas de deglución y ancianos, y favorecen el cumplimiento terapéutico. Además, esta combinación aúna la rapidez de acción del paracetamol con la acción más prolongada del clorhidrato de tramadol.

Objetivos: Demostrar la bioequivalencia entre los comprimidos bucodispersables de Paxiflas®, administrados con y sin agua, y los comprimidos de referencia, Zaldiar®, administrados con agua, en voluntarios sanos en ayunas.

Material y métodos: Estudio abierto, balanceado, aleatorizado, cruzado, de dosis única, de 3 tratamientos en 3 periodos y 3 secuencias, y con un tiempo de lavado de 7 días entre el periodo I y II y de 8 días entre el II y III. Los voluntarios fueron asignados al azar para recibir una dosis oral única (2 comprimi- dos) de Paxiflas®, administrado sin agua (producto A) y con agua (producto B), y Zaldiar® con agua. Se consideró bioequivalencia cuando el intervalo de confianza del 90 % (IC 90 %) de la rela- ción de la media geométrica de C_{max} y AUC_{0-t} entre el producto
en investigación A o B y el de referencia se encontró dentro del rango 80-12 % para (+) tramadol, (-) tramadol y paracetamol. El objetivo secundario consistió en evaluar la seguridad y tolerabilidad del producto en investigación A y B.

Resultados: Se evaluó bioequivalencia en 38 voluntarios para el producto A y en 39 para el producto B. Se alcanzaron concentraciones plasmáticas óptimas de (+) tramadol a las 0,75-3 h, para el producto A, a las 0,5-4 h para el B, y a las 0,5-3 h para el de referencia. En el caso del (-) tramadol se alcanzaron a las 0,75-3 h, para el A, a las 0,5-4 h para el B, y 0,5-3 h para el de referencia. Finalmente, para el paracetamol, se alcanzaron a las 0,25-2,5 h para el A, a las 0,5-2 h para el B, y a las 0,25-2,5 h para el de referencia. El IC 90 % de los parámetros principales se situó dentro de los rangos de aceptación del 80-125 % en los 38 voluntarios que tomaron el producto A y en los 39 que tomaron el B. Se reportaron un total de 6 acontecimientos adversos (AA) durante el estudio (dolor de ca- beza, mareo, dolor abdominal, picor en antebrazos y muslos, y elevado recuento de eosinófilos), de los que 3 eran esperados y posiblemente relacionados con el producto en investigación. La intensidad de los AA fue desde leve a moderada. No se observó ningún AA grave.

Conclusiones: Los datos del presente estudio demuestran la bioequivalencia entre los comprimidos bucodispersables de Paxiflas®, administrados con y sin agua en diferentes periodos, y los comprimidos de Zaldiar®, administrados con agua, en términos de velocidad y magnitud de la absorción en condiciones de ayuno.

Palabras clave: Bioequivalencia, tramadol, paracetamol, bucodispersable, dolor, tratamiento.

INTRODUCTION

Approximately 17% of the adult population in Spain suffers from chronic pain (1,2). For many patients, administering a single analgesic does not completely alleviate the pain (3), so combined therapies are used, requiring the administration of more than one drug. The association of two agents with complementary mechanisms of action that strengthen the analgesic effect and reduce the risk of developing possible adverse events (AEs) (4), may be a therapeutic option that improves ease of use and patients' compliance.

The combination of tramadol hydrochlorate and paracetamol is indicated for the symptomatic treatment of moderate to severe pain (5). Tramadol is an opioid analgesic that acts on the central nervous system. It consists of 2 enantiomers: the (+) isomer is predominantly active on the μ opioid receptor and the (-) isomer acts by inhibiting the re-uptake of norepinephrine and serotonin, strengthening the (+) isomer's analgesic effect (3,6). Paracetamol is a non-opioid analgesic whose mechanism of action is not fully known (7). It is believed to act at a central and peripheral level, inhibiting both prostaglandin synthesis and nitric oxide (8). The combination of both analgesics has proven to be synergic and, accordingly, more effective than each component separately. While the action of tramadol is slow and prolonged, the action of paracetamol is rapid and short-term (9). The combination's efficacy has been demonstrated in alleviating post-operative dental pain, in chronic lumbago and in acute pain caused by arthrosis (3,10-12). It also allows a reduction in dosage required for each of the agents and, therefore, a lower risk of producing AEs.

The World Health Organization (WHO) has found that up to 50% of patients do not comply with their treatment, negatively affecting its therapeutic effectiveness (13). In fact, the WHO considers non-compliance with treatment for chronic illnesses to be a "worldwide problem of alarming magnitude". One of the factors that affects adherence to a treatment is the pharmaceutical form used. Additionally, many patients have difficulty swallowing tablets or hard gelatin capsules (14). Compressed FDTs are uncoated tablets intended to be placed in the mouth, where they quickly dissolve without the need for water, which can help improve therapeutic compliance (15). Because there is no need to chew them nor take them with water, they can be taken at any time and anywhere, so they are ideally suited for active patients who do not have water at all times, for example young people, busy

people, people for whom water is not readily available (workers, sportspersons, etc.) or who travel frequently. In this last case, according to their destination, it may be more or less complicated to be able to access water, or even if they can, it may be not drinkable or in ideal conditions to drink (16). Furthermore, FDTs are appropriate for patients with difficulty swallowing (dysphagia), elderly people, people who are bedridden, stroke victims or patients with kidney failure, and for those with developmental or volitional problems in swallowing, such as pediatric, geriatric and psychiatric patients (15). It is also important to take into account patients with an aversion to tablets and capsules (16), as several studies have shown that 26%-50% of patients have problems when swallowing these pharmaceutical forms, mainly due to size, texture, shape or taste (14). Another advantage FDTs offer is that, as they dissolve so quickly in the mouth, they provide an improvement in bioavailability and rapid absorption through the mouth, pharynx and esophagus (15).

Paxiflas® is the combination of tramadol hydrochlorate / paracetamol (37.5 mg/325 mg) in the form of menthol-flavoured FDTs which dissolve in the mouth in less than 30 seconds. It has been marketed by Laboratorios Gebro Pharma S.A., and authorized by the Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency for Medicines and Health Products) in July 2016 (17). To register and authorize it for the market, a study was carried out to assess its bioequivalence compared to Zaldiar®, the tramadol/paracetamol (37.5 mg/325 mg) reference product in Spain and marketed by Grünenthal Pharma S. A.(18). The study's objective was to show bioequivalence between Paxiflas®, administered with and without water in different periods, and Zaldiar®, administered with water to healthy individuals on an empty stomach.

MATERIAL AND METHODS

Study design

The study was carried out between September and November 2014 following an open-label, balanced, randomized, crossover, single-dose design, with 3 treatments in 3 periods and different sequences (period I: September 25-27; period II: October 2-4; and period III: October 10-12), and with a washout period of 7 days between period I and II and of 8 days between II and III. The study's total duration was 17 days. Healthy volunteers were randomly assigned to receive a single oral dose (2 tablets) of the study product, Paxiflas®, administered without water (product A) or with water (product B), and Zaldiar® with water (reference product). Although the design was open-label, the sequence of administering the products was blind for the researcher. All volunteers signed informed consent before participating in the study. Both the final versions of the study protocol and of the informed consent were reviewed and approved by the Ethics Committee on Clinical Research in December 2013. All the procedures were carried out in accordance with the ethical principles laid down in the Declaration of Helsinki.

Participants

The study was carried out on a total of 42 healthy volunteers. The study's main inclusion criteria were: man or woman (non-pregnant) aged between 18 and 45 and weighing 50 kg; body mass index between 18.5 and 24.9 kg / m2; non-smoker; normal physical exam, normal vital signs (blood pressure, pulse, respiratory rate and axillary temperature) and normal clinical parameters (blood count, biochemistry, urine analysis, 12-lead ECG and chest x-ray); and with no background of alcoholism. Volunteers were admitted to the study center at least 11 hours before administering the drug and they remained in observation until 36 hours later. At the time of administering each product, volunteers were in overnight fast of, at least, 10 hours.

Products and treatments

The study product Paxiflas® (tramadol hydrochlorate 37.5 mg/paracetamol 325 mg in FDTs), marketed by Laboratorios Gebro Pharma S. A., was evaluated as administered with and without water. When administering without water (product A), volunteers drank 20 ml of water before administration with the purpose of moistening their mouth. Next, 2 tablets were placed on their tongue, which they sucked without chewing until their disintegration, ingesting the resulting suspension without additional water. In administration with water (product B), the resulting suspension was ingested with the help of 240 ± 2 ml water at room temperature. The reference product Zaldiar® (tramadol hydrochlorate 37.5 mg / paracetamol 325 mg in tablets) was administered with 240 ± 2 ml of water at room temperature.

Analytical determination

19 blood samples were taken from all volunteers 1 hour before administering each product up to 36 hours

afterwards (taken at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24 and 36 hours post-dose).

Pharmacokinetic evaluation and safety assessment

To evaluate the pharmacokinetics of study product A or B, each volunteer had to receive, at least, product A and the reference product, or B and the reference product, respectively. Plasma concentrations of (+) tramadol, (-) tramadol and paracetamol were measured by means of a validated analytical method of liquid chromatography-tandem mass spectrometry (LC/MS/MS). The relative bioequivalence of the study product (A and B) with respect to the reference product was evaluated by determining the following pharmacokinetic parameters for (+) tramadol, (-) tramadol and paracetamol: peak plasma concentration observed during the study (C_{max}), time to reach it (T_{max}), area under the plasma concentration-time curve for the last available concentration, using the trapezoidal rule (AUC_{0-t}), elimination rate constant (Ke) calculated by semi-logarithmic plot of the plasma concentration-time curve, using the least squares regression method, the area under the plasma concentration-time curve from zero to infinity (AUC_{0-}), calculated as AUC_{0-t} plus the addition of the ratio between the last available concentration and Ke, and mean life-time (t1/2), calculated as the relationship between the Napierian logarithm of 2 and Ke. Safety was assessed by means of the AE report, physical examination, vital signs, 12-lead ECG and clinical and laboratory tests.

Determination of sample size

In order to obtain a statistical power of 85% so that the 90% confidence interval (90% CI) of the relationship between log-transformed C_{max} and AUC values of the products compared fell within the accepted bioequivalence range of 80-125%, a number of 32 participants was considered. This estimate was based on the fact that zero relationship of the products compared would be of 0.95 and a maximum intra-individual variation of 25% (19). Finally, a total number of 42 participants was proposed, considering it was a study of 3 treatments and assuming the probability of discontinuation and withdrawal.

Statistical analysis

Bioequivalence was considered met when the 90% CI of the relationship of the geometric mean of C_{max} and AUC_{0-t} between the study product A or B and the reference product was within the range 80-125 % for (+) tramadol, (-) tramadol and paracetamol. Statistical bioequivalence was determined using the Schuirmann test (20). The geometric mean was obtained as the (exponential) antilogarithm of mean least squares of log-transformed values. An analysis of variance (ANOVA) was carried out to determine the treatment's possible effects, of the period and of the sequences in the pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-} untransformed and log-transformed for (+) tramadol, (-) tramadol and paracetamol. The difference of T_{max} between the different products was analyzed with the Wilcoxon non-parametric test. The 90% CI was calculated for the proportion of the geometric mean of least squares for (+) tramadol, (-) tramadol and paracetamol. Except where expressly stated, values are shown as the arithmetic mean together with the standard deviation (SD). Significant effect was established at a value $p \leq 0,05$. Randomization and pharmacokinetic analysis was carried out with the non-compartmental model using the SAS 9.2 program.

RESULTS

Since it is a crossover study, all subjects must take each of the products: A, B and reference. Out of the total 42 volunteers included in the study, 38 were administered, at least, product A, 39 product B, and 40 the reference product. Subject number 1 (sequence followed: B-reference-A), 4 (reference-A-B) and 22 (reference-A-B) completed at least 2 periods of the study, taking the reference product in one of the periods. Plasma samples of the 40 participants involved in one or both comparisons (A vs. reference and B vs. reference) were analyzed. Arrangement of subjects during the study is shown in Figure 1. Their mean age was 27.9 ± 5.6 years, with a mean weight of 61.4 ± 7.2 kg, and a mean body mass index of 22.3 ± 2.2 kg/m2. (+) tramadol, (-) tramadol and paracetamol were quickly absorbed after administration of each product. Appropriate plasma concentrations were reached for (+) tramadol at 0.75-3 h for product A, at 0.5-4 h for B, and at 0.5-3 h for the reference product (Figure 2). In the case of (-) tramadol, they were reached at 0.75-3 h for A, at 0.5-4 h for B, and 0.5-3 h for the reference product. Finally, for paracetamol, they were reached at 0.25-2,5 h for A, at 0.5-2 h for B, and at 0.25-2,5 h for the reference product.

Bioequivalence

Log-transformed pharmacokinetic parameters after administration of the study products (A and B) and the reference product are shown in Table I. In the analysis of (+) tramadol, (-) tramadol and paracetamol, the 90% CI of

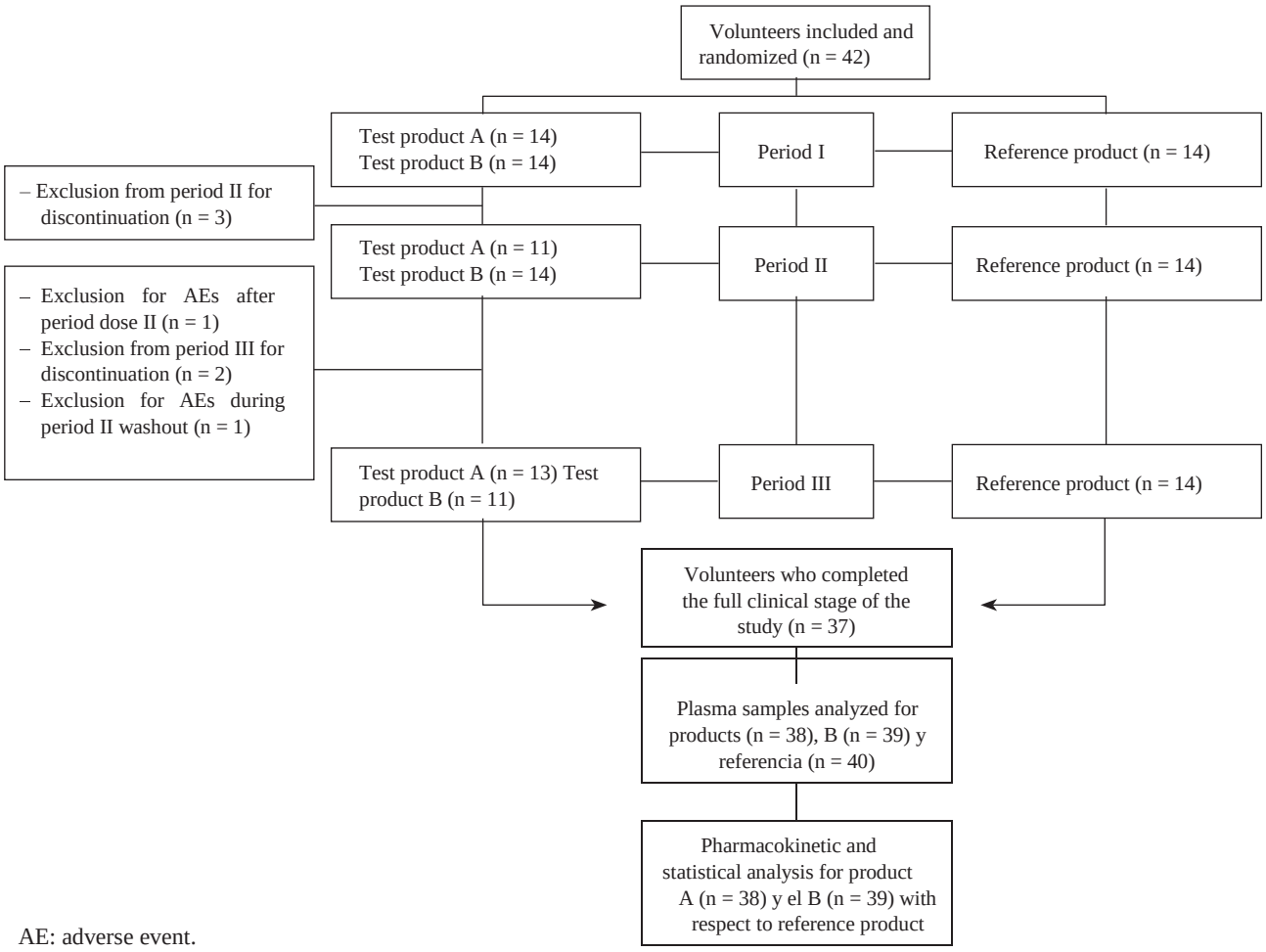

Fig. 1. Arrangement of subjects throughout the study.

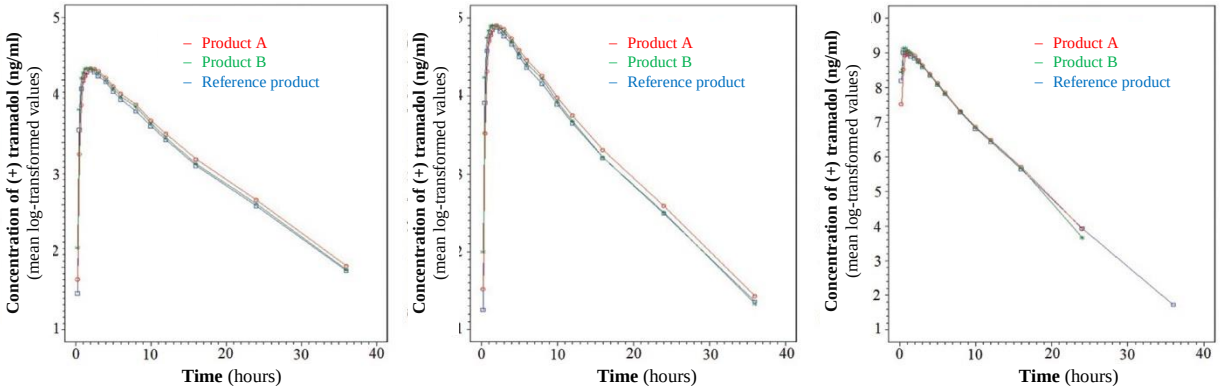

Fig. 2. Plasma concentration of (+) tramadol, (-) tramadol and paracetamol after oral administration of each of the products in the study.

the main parameters fell within the acceptance ranges of 80-125% in the 38 volunteers for product A and in 39 for product B. The relationship between product A or B and the reference product in the pharmacokinetic parameters for (+) tramadol, (-) tramadol and paracetamol calculated for a 90% CI are shown in Table II. No significant effect

TABLE I
ESTIMATED PHARMACOKINETIC PARAMETERS FOR THE DIFFERENT STUDY PRODUCTS

	C_{max} (ng/ml)	AUC_{0-t} (ng*h/ml)	$AUC_{0-\infty}$ (ng*h/ml)	T_{max} (h)	k_e (h^{-1})	$t_{1/2}$ (h)	Relationship $AUC_{0-t}/AUC_{0-\infty}$
(+) Tramadol							
Product A (n = 38)	206.57 ± 39.25	2.001.72 ± 517.11	2.094.82 ± 595.61	1.87 ± 0.74	0.09 ± 0.02	7.61 ± 1.44	96.12 ± 2.25
Product B (n = 39)	204.76 ± 40.09	1.963.09 ± 472.06	2.051.16 ± 539.13	1.63 ± 0.85	0.09 ± 0.02	7.70 ± 1.49	96.19 ± 2.21
Reference product (n = 40)	202.83 ± 45.93	1.862.45 ± 511.01	1.948.20 ± 583.35	1.63 ± 0.73	0.10 ± 0.02	7.53 ± 1.48	96.13 ± 2.36
(-) Tramadol							
Product A (n = 38)	156.06 ± 29.60	1.399.86 ± 346.69	1.446.57 ± 387.25	1.88 ± 0.73	0.10 ± 0.02	6.90 ± 1.24	97.17 ± 1.74
Product B (n = 39)	153.88 ± 29.37	1.362.89 ± 307.34	1.404.57 ± 336.46	1.64 ± 0.85	0.10 ± 0.02	6.95 ± 1.18	97.31 ± 1.50
Reference product (n = 40)	153.16 ± 35.24	1.304.54 ± 359.93	1.348.67 ± 399.87	1.60 ± 0.71	0.10 ± 0.02	6.87 ± 1.35	97.13 ± 1.89
Paracetamol							
Product A (n = 38)	10.214.72 ± 2.648.54	41.465.99 ± 11.790.48	43.297.51 ± 12.242.16	1.28 ± 0.63	0.20 ± 0.07	3.90 ± 1.44	95.75 ± 1.65
Product B (n = 39)	10.466.18 ± 2.905.11	42.494.81 ± 12.348.55	44.347.13 ± 12.806.25	0.85 ± 0.41	0.21 ± 0.06	3.66 ± 1.17	95.78 ± 1.37
Reference product (n = 40)	11.322.92 ± 3.336.95	41.198.84 ± 11.808.38	43.042.33 ± 12.220.66	1.05 ± 0.68	0.20 ± 0.07	3.91 ± 1.50	95.68 ± 1.20

C_{max}: peak concentration. AUC_{0-t}: area under the plasma concentration-time curve for the last concentration available. $AUC_{0-\infty}$: area under the plasma concentration-time curve from zero to infinity. T_{max}: time for peak concentration. K_e: elimination constant. $t_{½}$: mean life-time.

was detected regarding the sequence in the log-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-} for (+) tramadol, (-) tramadol and paracetamol. The analysis to identify effects of the treatment, period and sequence in pharmacokinetic parameters for (+) tramadol, (-) tramadol and paracetamol are shown in Table III. Effects were observed regarding treatment and period, mainly for (+) tramadol and (-) tramadol. The statistical power for log-transformed C_{max} and AUC_{0-t} was greater than 80% for (+) tramadol, (-) tramadol and paracetamol.

Safety profile

A total of 6 AEs were reported during the study in 6 participating subjects: headache (2.4% of the total number of volunteers), dizziness (2.%), abdominal pain (2.4%), itch on forearms (2.4%) and thighs (2,4%), and high eosinophil count (2,4%). Among the AEs, 3 were expected and possibly related to the product under study. AE intensity was from slight to moderate. No serious AE was observed.

DISCUSSION

The demand for FDTs has grown over the last decade (15). The term FDT refers to the fact that, when tablets are placed in the mouth, they dissolve in less than 3 minutes before swallowing (21). As water is not necessary in order to take them, their administration is intended for active patients who do not have water at all times, for example busy people, workers, sportspersons or people who travel frequently (16). FDTs are also ideal

TABLE II

ANALYSIS OF BIOEQUIVALENCE BETWEEN PRODUCTS A OR B AND THE REFERENCE PRODUCT FOR (+) TRAMADOL, (-) TRAMADOL AND PARACETAMOL WITH A 90% CONFIDENCE INTERVAL

Product A versus *reference*		*Geometric mean*		*Relationship (%)*	*90 %CI (80-125 %)*
		Product A	*Reference product*	*A/Reference*	
AUC_{0-t} (ng*h/ml)	(+) Tramadol	1,928.87	1,802.37	107.02	104.42-109.68
	(-) Tramadol	1,352.16	1,262.74	103.05	104.31-109.93
	Paracetamol	40,280.81	39,756.24	101.32	99.35-103.33
C_{max} (ng/ml)	(+) Tramadol	203.75	198.06	102.88	104.42-109.68
	(-) Tramadol	154.06	149.50	103.05	98.03-108.33
	Paracetamol	9,940.95	10,856.90	91.56	84.57-99.14
Product B versus *reference*		*Geometric mean*		*Relationship (%)*	*90%CI (80-125 %)*
		Product B	*Reference product*	*B/Reference*	
AUC_{0-t} (ng*h/ml)	(+) Tramadol	1,904.43	1,802.37	105.66	103.12-108.27
	(-) Tramadol	1,330.69	1,262.74	101.73	96.82-106.90
	Paracetamol	41,055.51	39,756.24	103.27	101.28-105.30
C_{max} (ng/ml)	(+) Tramadol	202.08	198.06	102.03	97.15-107.15
	(-) Tramadol	152.09	149.50	101.73	96.82-106.90
	Paracetamol	10,171.99	10,856.90	93.69	86.59-101.37

AUC_{0-t}: area under the plasma concentration-time curve for the last concentration available. C_{max}: peak concentration.
90% CI: confidence interval 90%.

TABLE III

STATISTICAL ANALYSIS TO DETERMINE POSSIBLES EFFECTS OF THE TREATMENT, PERIOD AND SEQUENCIE IN PHARMACOKINETIC PARAMETERS FOR (+) TRAMADOL, (-) TRAMADOL AND PARACETAMOL

	P values of the ANOVA								
	Treatment			*Period*			*Sequence*		
	(+) Tramadol	(-) Tramadol	Paracetamol	(+) Tramadol	(-) Tramadol	Paracetamol	(+) Tramadol	(-) Tramadol	Paracetamol
$C_{máx}$	0.6157	0.6038	0.1635	0.1975	0.1906	0.1091	0.7894	0.6645	0.7286
AUC_{0-t}	< 0.0001	0.0001	0.0263	0.0153	0.1295	0.1431	0.3247	0.2861	0.7283
$AUC_{0-\infty}$	< 0.0001	0.0002	0.0351	0.0084	0.1082	0.0811	0.3631	0.3126	0.6922

$C_{máx}$: peak concentration. AUC_{0-t}: area under the plasma concentration-time curve for the last concentration available.
$AUC_{0-\infty}$: area under the plasma concentration-time curve from zero to infinity.

for patients with problems swallowing, the elderly, bed-ridden, stroke victims (15) and any person who has problems swallowing tablets or capsules (14). In a questionnaire carried out on 3,279 doctors to find out their opinion of what patients think regarding the prescription of drugs, FDTs scored highest in attributes associated with oral forms (14). In fact, 68.3% and 49.3% highlighted speed of action and easy use, respectively, as FDTs' main attributes. Capsules and tablets, however, were the forms that scored worst regarding speed of action. Additionally, the lack of difficulty in swallowing is a factor that positively influences patients' compliance with their therapy.

In turn, if we include the circumstance of combining two analgesic agents in one single tablet, we offer more convenient dosage and reduce the number of drugs to ingest, which can facilitate therapeutic compliance (4).

According to the WHO, "Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and their bioavailabilities, in terms of peak C_{max}, T_{max} and total exposure (area under the curve (AUC)), after administration in the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same" (22). In the study presented, the estimated pharmacokinetic parameters fell within the 90% CI (80-125%) established to confirm bioequivalence. Statistical power was above superior 80% for (+) tramadol, (-) tramadol and paracetamol. Additionally, the diagram showing the concentration of Paxiflas® in plasma over time (with and without water) coincided with the values of Zaldiar®. Although significant effects were not detected as regards sequence in product administration, effects of the treatment and of the period were observed in certain log-transformed pharmacokinetic parameters, such as AUC_{0-t}. One possible explanation for the effect of the treatment could be the low intra-individual variation of participants. With respect to the period, it is an effect that is commonly seen in crossover bioequivalence studies after comparing pharmacokinetic parameters of one period with regard to another, regardless of the treatment administered. This effect of the period cannot be wholly eliminated due to the existence of factors beyond the control-

of the clinical study's implementation, such as for example the mental state of individuals, which may vary

in different periods of the study, thus affecting bowel movement and the drug's absorption. Nevertheless, the decision of bioequivalence has been based on the Schuirmann test and the 90% CI falls within the criteria for acceptance, that is, 80-125%, so in the authors' opinion, the results regarding the effects of treatment and period have no clinical significance. Finally, compressed Paxiflas® FDTs were well tolerated, administered with and without water. AEs reported were the same as described for the reference product (18).

CONCLUSION

The data of this study demonstrates the bioequivalence of Paxiflas® FDT (tramadol hydrochlorate 37.5 mg/paracetamol 325 mg), administered with and without water, and Zaldiar® tablets, administered with water, in terms of speed and magnitude of absorption on an empty stomach. Paxiflas® could facilitate, due to its ease of use, therapeutic compliance, especially among active patients and in patients with problems swallowing.

BIBLIOGRAFÍA

1. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. Eur J Pain 2006;10:287-333. DOI: 10.1016/j.ejpain.2005.06.009.
2. Langley P, Ruiz-Iban M, Molina J, De Andres J, Castellón J. The prevalence, correlates and treatment of pain in Spain. J Med Econ 2011;14:367-80. DOI: 10.3111/13696998. 2011.583303.
3. McClellan K, Scott L. Tramadol/Paracetamol. Drugs 2003;63:1079-86. DOI: 10.2165/00003495-200363110-00007.
4. Raffa R. Pharmacology of oral combination analgesics: Rational therapy for pain. J Clin Pharmacol Ther 2001; 26:257-64. DOI: 10.1046/j.1365-2710.2001.00355.x.
5. Dhillon S. Tramadol/paracetamol fixed-dose combination: a review of its use in the management of moderate to severe pain. Clin Drug Investig 2010;30:711-38. DOI: 10.2165/ 11205830-000000000-00000.
6. Raffa R, Friderichs E, Reimann W, Shank R, Codd E, Vaught J. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. J Pharmacol Exp Ther 1992;260:275-85.
7. Smith H. Potential analgesic mechanisms of acetaminophen. Pain Physician 2009;12:269-80.
8. Anderson B. Paracetamol (acetaminophen): mechanisms of action. Paediatr Anaesth 2008;18:915-21. DOI: 10.1111/ j.1460-9592. 2008.02764.x.
9. Mejjad O, Serrie A, Ganry H. Epidemiological data, efficacy and safety of a paracetamol-tramadol fixed combination in the treatment of moderate-to-severe pain. SALZA: a post-marketing study in general practice. Curr Med Res Opin 2011;27:1013-20. DOI: 10.1185/03007995.2011.565045.
10. Medve R, Wang J, Karim R. Tramadol and acetaminophen tablets for dental pain. Anesth Prog 2001;48:79-81.
11. Silverfield J, Kamin M, Wu S-C, Rosenthal N. Tramadol/ acetaminophen combination tablets for the treatment of osteoarthritis flare pain: a multicenter, outpatient, randomized, double-blind, placebo-controlled, parallel-group, add-on study. Clin Ther 2002;24:282-97. DOI: 10.1016/ S0149-2918(02)85024-X.
12. Peloso P, Fortin L, Beaulieu A, Kamin M, Rosenthal N. Analgesic efficacy and safety of tramadol/acetaminophen combination tablets (Ultracet) in treatment of chronic low back pain: a multicenter, outpatient, randomized, double blind, placebo controlled trial. J Rheumatol 2004;31:2454-63.
13. Organización Mundial de la Salud. Adherencia a los tratamientos a largo plazo. Pruebas para la acción; 2004. Disponible en: http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&gid=18722&Itemid=270. (Acceso Octubre, 2016).
14. Artés M, de Agustín T, Galván J, Heras M. Influencia y valor de las preferencias del paciente en la prescripción médica. Estudio de opinión entre profesionales de la salud. Salud rural 2007;24:37-47.
15. Parkash V, Maan S, Deepika, Yadav S, Hemlata, Jogpal V. Fast disintegrating tablets: Opportunity in drug delivery system. J Adv Pharm Technol Res 2011;2:223-35. DOI: 10.4103/2231-4040.90877.
16. Roger Reig A, Plazas Fernández M, Galván Cervera J, Heras Navarro J, Artés Ferragud M, Gabarrón Hortal E. Acceptance survey of a fast dissolving tablet pharmaceutical

formulation in allergic patients. Satisfaction and expectancies. Allergol Immunopathol (Madr) 2006;34:107-12.
17. Paxiflas. Prospecto: información para el usuario. Disponible en: http://www.aemps.gob.es/cima/pdfs/es/p/80834/Prospecto_80834.html.pdf. (Acceso Octubre, 2016).
18. Zaldiar. Prospecto: información para el usuario. Disponible en: https://www.aemps.gob.es/cima/pdfs/es/p/70584/70584_p.pdf. (Acceso Octubre, 2016).
19. Public Assessment Report. Scientific Discussion Zaldiar/Ixprim 37.5 mg/325 mg effervescent tablets 37.5 mg tramadol hydrochloride and 325 mg Paracetamol, FR/H/211-212/02/DC. Grünenthal, 2008. Disponible en: db.cbg-meb.nl/Pars/h101592.pdf. (Acceso Octubre, 2016).
20. Schuirmann D. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability. J Pharmacokinet Biopharm 1987;15:657-80. DOI: 10.1007/BF01068419.
21. Council of Europe. European Pharmacopoeia. 5th Ed. MainVolume 5.0. Strasbourg, France: 2005. pp. 628.
22. World Health Organization. Expert Committee on Specifications for Pharmaceutical Fortieth Report. Genova, 2006. Disponible en:apps.who.int/medicinedocs/documents/s14091e/s14091e.pdf (Acceso Octubre, 2016).