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Article

Analysis of the effect of *in vitro* dissolution on the pharmacokinetics of albendazole

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Albendazole is an anthelmintic drug commonly used in parenchymal neurocysticercosis and cystic echinococcosis. The aim of this study was to explore whether disparities in the dissolution profiles of albendazole products lead to significant differences in pharmacokinetic parameters. Three generic products and the innovator were evaluated *in vitro*. Quality control tests were performed, and dissolution profiles were obtained according to the Mexican Pharmacopeia. Although all products passed the quality control tests, none of the generic products complied with the similarity factor (f_2). The product with the lowest f_2 value in respect to the reference was chosen for *in vivo* evaluation. The study was carried out in 12 healthy volunteers who received 400 mg of the generic or reference product according to a crossover design. No significant differences were found in C_{max} and AUC for albendazole and its main metabolite, albendazole sulfoxide, between products. Two absorption peaks were observed in the pharmacokinetic profile, and a population (22%) with different absorption rates and delay time for the the second peak was found. Based on the results, due to the high variability in the absorption process the differences observed *in vitro* could not be observed *in vivo*.

Keywords: Albendazole. Quality control. Dissolution. Pharmacokinetic modeling.

INTRODUCTION

Albendazole (ALB) is a broad-spectrum anthelmintic drug used to treat parenchymal neurocysticercosis and cystic echinococcosis. Chewable tablets of ALB are included in the WHO´s list of Essential Medicines (World Health Organization, 2021). In Mexico, ALB is the drug of choice for treating parasitic diseases and is available in the National Essential Medicines List as tablets or suspension (Compendio Nacional de Insumos para la Salud, version 2023).

ALB is a highly hydrophobic drug that is poorly absorbed in the gastrointestinal tract, partially due to its low solubility (Mirfazaelian, Rouini, Dadashzadeh, 2002). Even though ALB is widely used in Latin American countries, with the exception of Brazil and Mexico, a bioequivalence study is not required for generic albendazole products; however, the products must comply with the pharmacopeial requirements. The Mexican Pharmacopoeia, the Brazilian Pharmacopoeia, and the Argentine National Pharmacopoeia (Farmacopea de los Estados Unidos Mexicanos, 2018; Farmacopeia Brasileira, 2019; Farmacopea Argentina, 2013) contain a monograph for ABZ tablets, that includes a required dissolution test. Other countries have adopted the USP Pharmacopoeia.

While a single-point dissolution test is an important tool to ensure the quality of drug products, dissolution profiles are essential during the formulation development of generic products before bioequivalence studies are performed. To date, different reports indicate that the dissolution profiles of ABZ generic products are different from those obtained with the innovator product using the Pharmacopeial conditions. Sitre and Kamble (2021)

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performed several experiments to develop and optimize drug release from ABZ tablets using a factorial design. Risk assessment showed that polyvinylpyrrolidone, sodium lauryl sulfate and sodium starch glycolate had an impact on the dissolution profile. The authors highlighted that utilizing different excipients could lead to variations in dissolution through this study. Hurtado *et al*. (2003) evaluated the dissolution of ABZ of three different generic products and the innovator, using USP apparatus 2 and apparatus 4. Differences in the dissolution profiles were found in both systems by the authors. In a previous study, we evaluated the dissolution behavior of six generic ABZ products. The results showed that only 2 products were comparable to the innovator (Mayet *et al*., 2008). Another study showed that the dissolution profile of a generic albendazole 200 mg product from Peru did not comply with the f_2 test and therefore was not similar to that of the innovator (Alva *et al*., 2015). Currently, it remains unknown whether differences in the dissolution profiles obtained using the Pharmacopeial test impact the *in vivo* results of ABZ tablets; therefore, the main objective of the present study was to determine whether the *in vitro* dissolution release profile could be representative of the *in vivo* pharmacokinetic behavior of albendazole.

MATERIAL AND METHODS

Chemicals

Albendazole, albendazole sulfoxide and carbamazepine (internal standard) were obtained from Sigma–Aldrich. HPLC-grade solvents were purchased from J.T. Baker. Drug release media and buffer were prepared using hydrochloric acid and monobasic ammonium phosphate (J.T. Baker). Water was obtained from a Milli-Q (Merck Millipore, Germany) water purification system.

Drug products

For the *in vitro* studies, four different products (tablets, 200 mg) marketed in Mexico were evaluated. One was the reference product (A) (Zentel ®, Sanfer, Mexico) and the other three were generic test products (B, C, and D). All products were purchased directly from the pharmacy.

In vitro studies

Quality control

To assure the quality of the products, the following tests were performed according to the Mexican Pharmacopoeia monograph for ABZ tablets: assay, test to determine uniformity of dosage units and dissolution studies (Farmacopea de los Estados Unidos Mexicanos, 2018).

For the assay, the content of the tablets was weighed accurately and ground into a fine powder. A weighed portion of the powder, equivalent to 100 mg of albendazole, was transferred to a 50-mL volumetric flask. Then, 5 mL of acidified methanol (methanol and sulfuric acid, 99:1, v/v) and 20 mL of methanol were added and shaken by mechanical means for 15 minutes, diluted with methanol to volume, mixed and filtered. A volume of 5 mL of the filtrate was taken and diluted to 50 mL with methanol. Three samples were analyzed by HPLC and compared with a standard solution of albendazole (0.2 mg/mL). Methanol and ammonium monobasic phosphate solution (0.01 M) in a ratio of 60:40 (v/v) were used as the mobile phase. The flow rate was set at 2 mL/min and the injection volume of the sample was 20 µL. Chromatographic separation was performed using a Shimadzu HPLC with a UV–Vis detector set to a wavelength of 254 nm.

To determine the uniformity of dosage units, 10 units were analyzed individually. Each tablet was placed in a 500-mL volumetric flask, and 300 mL of acidified methanol (methanol-hydrochloric acid, 98:2, v/v) was added, shaken mechanically for 30 min, and diluted to volume with acidified methanol. The absorbances of the test solutions were determined at approximately 308 and 380 nm using 0.1 N sodium hydroxide as a blank. The percentage of labeled albendazole was determined by comparing the absorbance of the samples with a standard solution containing 9 µg/mL of albendazole. Finally, the acceptance value ($L1 \leq 15$) of uniformity of dosage units was calculated.

Dissolution studies

The release of ABZ was evaluated using a USP 2 dissolution apparatus (VK 7000, Vankel, USA) at 50 rpm with 900 mL of HCl 0.1 N, pH 1.2, as dissolution media with twelve replicates at 37 ± 0.5 °C. Samples of 5 mL were withdrawn at 10, 15, 20, 30, 45, 60 and 90 minutes without media replacement and filtered through a 0.45 µm Durapore® filter (Millipore Sigma, USA). An aliquot was diluted with HCl 0.1 N and assayed using a previously validated spectrophotometric method at 291 nm (UV–VIS spectrophotometer, Shimadzu, Japan).

The method was linear from 3-26 µg/mL and intra- and interday coefficients of variation were less than 2%.

In vivo study

For the *in vivo* study, the product with the greatest difference in the dissolution profile was selected. The study was conducted in 12 healthy adult subjects using Zentel® (200 mg, 2 tablets) as the reference product. The study was performed in accordance with the ethical standards formulated in the Helsinki Declaration, and the protocol was approved by the Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez (INNN, protocol number 19/18). All the subjects provided their written informed consent prior to study enrollment.

An open-label study was conducted according to a randomized, two-treatment, two-period, two-sequence, crossover design with a 1-week washout period between doses. Subjects were randomly divided in into two groups. In the first period of the study, subjects in Group 1 received a single oral dose of 400 mg (two 200 mg tablets) of the reference product while Group 2 received the same dose of the test product. In the second period of the study, the treatments were crossed over so that subjects in Group 1 received the test product and subjects in Group 2 received the reference product, with a one-week washout period between doses.

After the subjects underwent fasting for 10 h, the products were administered with 250 mL of water. No food intake was permitted for 4 hours after dosing. At this time, a standard meal was provided. Blood samples were collected from the antecubital vein in heparinized tubes prior to dosing (0 h) and at the following times: 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24 and 48 hours after dosing. Samples were centrifuged at 3000 rpm for 10 min. Plasma was separated and stored at -70 °C until analysis.

Bioanalytical method

Plasma concentrations of albendazole and albendazole sulfoxide were determined by a liquid chromatographic method coupled with tandem mass spectrometry (LC–MS/MS), which was developed and validated before the *in vivo* study was performed. The LC–MS/MS system consisted of an Agilent 1100 HPLC (quaternary pump and autosampler) (Agilent, USA) coupled to a turbo ion spray ionization-triple quadrupole mass spectrometer, API 3200 (ABSciex, Germany), with positive ion electrospray ionization using multiple reaction monitoring (MRM) mode. The analytical column was a Gemini® C_{18} (5 µm, 150 mm x 4.6 i.d., Phenomenex) attached to a precolumn (Phenomenex C_{18} ODS). The mobile phase consisted of a mixture of methanol:20 mM and formic acid (70:30, v/v). Table I shows the tandem mass spectrometric parameters.

TABLE I - Tandem mass spectrometric parameters of albendazole, albendazole sulfoxide and IS

Compound	Mol wt (g/mol)	Protonated ion (*m/z*)	Fragment (*m/z*)	CE (eV)	DP (V)	EP (V)	CXP (V)
Albendazole	265.3	266.3	234.0	25.0	34.0	4.5	3.0
Albendazole sulfoxide	281.0	282.0	240.0	16.0	20.0	5.0	3.0

TABLE I - Tandem mass spectrometric parameters of albendazole, albendazole sulfoxide and IS

Compound	Mol wt (g/mol)	Protonated ion (*m/z*)	Fragment (*m/z*)	CE (eV)	DP (V)	EP (V)	CXP (V)
Carbamazepine (IS)	238.0	237.0	194.1	22.0	43.0	4.0	3.0

Mol wt- molecular weight; CE- Collision energy; eV- Electron volt; DP- Declustering potential; V- Volt; EP- Entrance potential; CXP- Collision cell exit potential; IS- Internal standard

For the assay, plasma samples (300 µL) were transferred to a polyethylene tube and spiked with 100 µL of internal standard (carbamazepine, 400 ng/mL). After the samples were vortexed for 1 min, 5 mL of ether:dichloromethane:chloroform (60:30:10, v/v/v) was added. The samples were vortexed and centrifuged at 3000 rpm for 20 min. The organic layer was transferred to a clean glass assay tube and evaporated to dryness under a nitrogen stream at 60 °C. The residue was then reconstituted with 100 µL of methanol:water (70:30, v/v) and 10 µL was injected into the chromatographic system. The method was linear in the range of 1.5–100 ng/mL for albendazole and from 10–1500 ng/mL for albendazole sulfoxide. Intraday and interday coefficients of variation were less than 15%. The recovery for albendazole ranged from 81-90% and that for albendazole sulfoxide ranged from 84-90%.

Data analysis

In vitro studies

A model-independent analysis using the DDSolver complement was performed to determine the dissolution efficiency (DE), mean dissolution time (MDT), and mean residence time (MRT). The similarity factor, f_2, was calculated using the following equation:

$$f2 = 50 \cdot log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)^2\right]^{-0.5} \times 100\right\}$$

where n is the number of dissolution sampling times and Rt and Tt are the mean percent dissolved at each time point (t) for the reference and test products, respectively.

To determine the kinetics of drug release, data were fitted to the following dissolution models: first order and Weibull. The determination coefficient and the Akaike criterion (AIC) were used to select the optimal model.

In vivo study

Pharmacokinetic parameters of albendazole and albendazole sulfoxide were estimated by a non-compartmental analysis using WinNonlin Version 5.0.1 (Pharsight Corp., USA). The following pharmacokinetic parameters were determined: maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the curve calculated with the linear trapezoidal method from 0 h to the time of the last quantifiable plasma concentration ($AUC_{0\text{-}tlast}$), AUC from 0 h to time infinity ($AUC_{0\text{-}inf}$) and terminal elimination half-life ($t_{1/2}$).

A population pharmacokinetic analysis for ABZ was also performed by the nonlinear mixed-effects modeling approach using MONOLIX 2021R software.

RESULTS

In vitro studies

Table II shows that the products evaluated complied with quality control specifications of the Mexican Pharmacopeia. The products generated similar results with the assay (within 100.4–102.3%) and the uniformity of dosage units test. Additionally, the mean percentage dissolved at 30 min ranged from 80 to 96% (not less than 80% of the labeled amount dissolved).

TABLE II - Quality control and dissolution parameters of 200 mg albendazole tablets

Product	Assay (%)	Uniformity of dosage units (%)	Dissolution at 30 min (%)	MRT	MDT	DE	f_2
A	100.4 ± 3.3	100.4 ± 1.3	96.9 ± 1.8	5.016	9.03	0.9086	
B	102.3 ± 2.4	102.3 ± 0.8	80.0 ± 3.4	23.18	16.67	0.7674	35.48
C	101.6 ± 2.5	101.6 ± 1.9	88.3 ± 4.3	23.25	11.07	0.8195	49.10
D	100.4 ± 0.9	100.4 ± 0.6	85.6 ± 3.6	19.90	13.20	0.8171	44.45

MRT- Mean residence time; MDT- Mean dissolution time; DE- Dissolution efficiency; f_2- similarity factor

Dissolution profiles are shown in Figure 1. In all tests the coefficient of variation at the different sampling time points was less than 10%. The similarity factor (f_2) was determined as a measure of the closeness in the percent of dissolution between two curves. The acceptance criterion by the regulatory agencies is $f_2 \geq 50$. Table II shows the results obtained from the f_2 test as well the dissolution parameters DE, MDT and MRT. Considering that product B presented the lowest f_2 and DE values as well as the highest difference in MDT between the products, it was selected for the *in vivo* study.

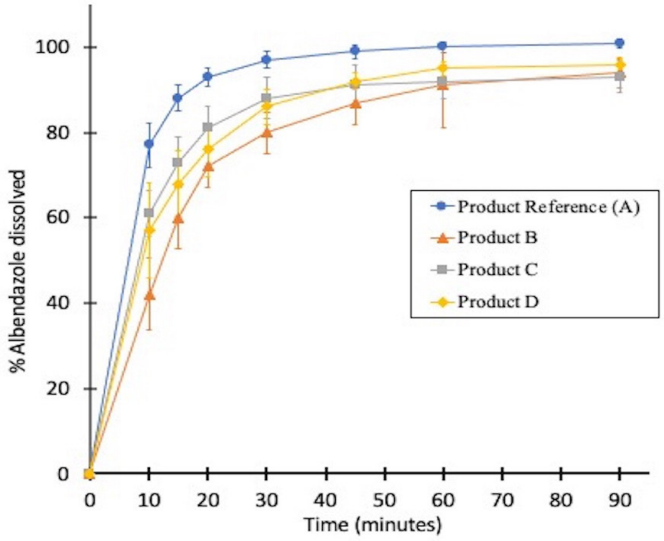

FIGURE 1 - Dissolution profiles of 200 mg albendazole tablets (n = 12).

In vivo study

Figure 2 shows the concentration-time profiles of ABZ and ABZSO generated after 400 mg was administered orally. Low concentrations of the parent drug were detected in plasma during the 24 h period, while the main metabolite ABZSO was quantified up to 48 h.

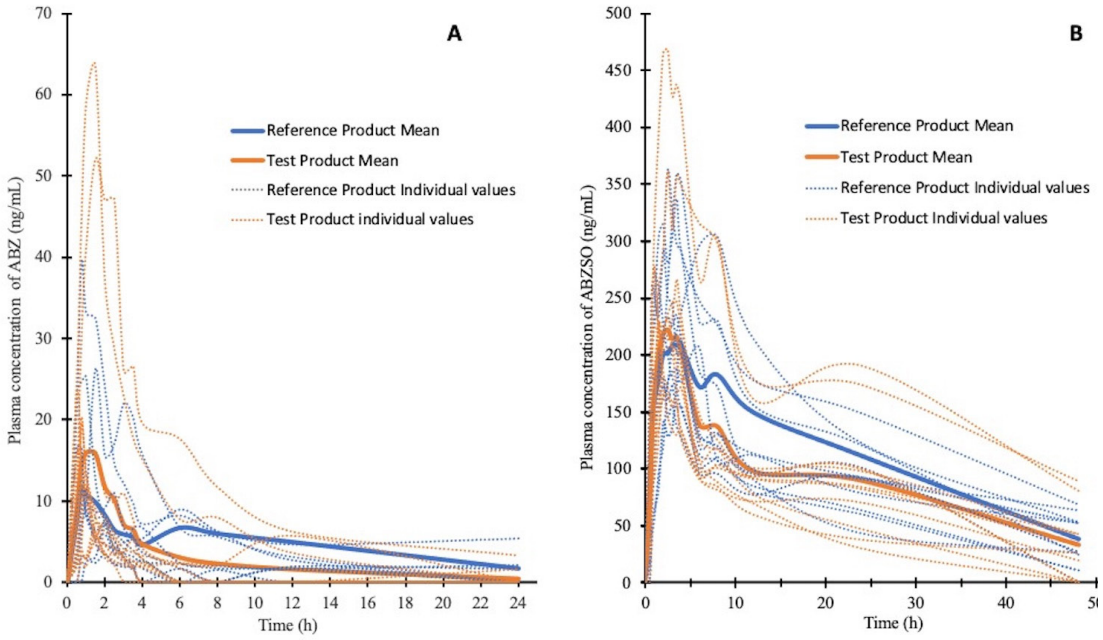

FIGURE 2 - Individual (dotted lines) and mean (continuous lines) of plasma concentration-time profiles for A) albendazole, B) albendazole sulfoxide in healthy volunteers after an oral administration of 400 mg ABZ (n = 12).

The pharmacokinetic parameters for ABZ and ABZSO are shown in Table III. Although the AUC values were greater for the reference product than for the test product, no significant differences were found for ABZ or ABZSO because of the high interindividual variability. Furthermore, no significant differences in C_{max} were found (p<0.05).

TABLE III – Mean pharmacokinetic parameters of albendazole and albendazole sulfoxide after the administration of a dose of 400 mg of the test and reference products

Parameter	Albendazole		Albendazole sulfoxide	
	Reference A	Test B	Reference A	Test B
C_{max} (ng/mL)	18.48 ± 13.89	20.97 ± 18.23	288.91 ± 101.39	252.91 ± 87.30
t_{max} (h)	2.08 ± 1.93	1.16 ± 0.48	4.08 ± 3.03	2.21 ± 0.86
$AUC_{0\text{-last}}$ (ngh/mL)	98.00 ± 180.45	62.66 ± 86.88	5303.19 ± 3131.87	4189.71 ± 2280.22
$AUC_{0\text{-inf}}$ (ngh/mL)	117.75 ± 204.82	74.51 ± 94.83	6781.75 ± 3754.69	5615.32 ± 2945.33
$t_{1/2}$ (h)	3.93 ± 3.33	3.67 ± 3.55	20.11 ± 8.58	21.03 ± 7.03
MRT_{inf} (h)	6.05 ± 4.60	5.13 ± 3.85	28.49 ± 11.85	29.53 ± 8.97

C_{max}- Peak plasma drug concentration; t_{max}- Time to reach peak plasma drug concentration; $AUC_{0\text{-last}}$- Area under the plasma drug concentration-time curve to the last point; $AUC_{0\text{-inf}}$- Area under the plasma drug concentration-time curve to infinitum; $t_{1/2}$- Terminal elimination half-life; MRT_{inf}- Mean residence time. Mean ± SD; n = 12

DISCUSSION

It has been shown that albendazole is a class 2 drug and its rate of absorption is limited by its solubility. In Mexico, there are different generic products containing this drug; thus, through the present study, we obtained more information about the *in vitro* performance of the products. The reference product showed a very rapid dissolution behavior (≥ 85% at 15 min), and these results are consistent with a previous study performed in our laboratory (Mayet *et al*., 2008). With respect to the generic products, none of them complied with the f_2 test, indicating that the dissolution profiles were not similar to the reference product. Additionally, differences in DE, MDT and MRT between the generics and the reference product were found, denoting differences in the release profiles of ABZ tablets (Table II).

When the kinetics of drug release were evaluated using model-dependent methods, the results showed that the Weibull model provided the best adjustment with higher determination coefficients (r^2) and the lowest AIC values. The variables related to this model are parameter (α), which defines the time scale of the process; the localization parameter (Ti), which represents the latency time of the release process; and parameter (β), which characterizes the shape of the dissolution curve (if β = 1 exponential shape, if β<1 parabolic and a β>1, sigmoidal) (Langenbucher, 1972). Table IV shows the differences in shape (β) and localization parameter (Ti) between products. The largest difference was observed in the scale parameter (α) for product B, supporting the selection of this product for the *in vivo* study.

TABLE IV – *In vitro* dissolution data modeling of reference and test products of ABZ using DDSolver

		Product			
Model	Parameter	Reference	B	C	D
Weibull	α	2.1505	2.6401	1.3421	2.0852
	β	0.6238	0.4647	0.3161	0.3385
	Ti	3.6676	7.822	7.8703	7.5491
	R^2	0.9998	0.9992	0.9986	0.9987
	AIC	7.9686	18.903	23.914	21.745
First order	k1	0.143	0.056	0.085	0.052
	R^2	0.9991	0.9834	0.9738	0.9873
	AIC	17.465	40.091	43.518	51.232

α- Scale parameter; β- Shape parameter; Ti- location parameter; AIC- Akaike information criterion

In the pharmacokinetic study, a high interindividual variability in C_{max} and AUC was found for both the reference and the test product for ABZ and ABZSO (Figure 2). The data showed that for C_{max}, the coefficients of variation were higher than 70% for ABZ and 30% for ABZSO. Variability was higher for AUC. The variability was similar to that reported previously by other authors. Rigter *et al*. (2004) conducted a bioavailability study in 12 healthy volunteers and compared three new albendazole formulations with a commercially available tablet. For the commercial tablet, the mean and standard deviation values of C_{max} and AUC for ABZSO were 0.30 mg/L (14) and 4.20 mg•h/L (1.85), respectively, which correspond to a variability of approximately 40%. For the new

formulations, even when absorption was improved, the variability remained with values higher than 30% in both parameters. Ochoa *et al*. (2021) compared the bioequivalence of two albendazole formulations in 12 healthy volunteers after a single oral dose of 400 mg administered with a low-fat and a high-fat breakfast. The results showed that the C_{max} values for ABZ were clearly influenced by the type of meal. The mean values and standard deviations for the reference and test products were 57.5 (52.3) and 53.4 (51.4) ng/mL, respectively, for low-fat breakfast and 128.9 (160.4) and 123.9 (103.9) ng/mL, respectively, after a high-fat breakfast. With these results, an interindividual variability above 80% can be observed. For the AUC, the variability was similar.

To explain the variability observed in the absorption phase, a nonlinear mixed-effects modeling using the stochastic approximation expectation maximization algorithm (SAEM) implemented in Monolix 2021R was performed. The structural pharmacokinetic models consisting of one compartment with first-order absorption and elimination and one compartment with first-order double absorption were evaluated and compared (Godfrey *et al*., 2011). The Akaike information criterion (AIC) and the Bayesian information criterion (BIC) were used to select the best model. The base model and error model (combined additive and proportional and proportional and exponential) were selected based on the diagnostic plots, and the change in the objective function value (OFV) was calculated as -2* loglikelihood. Between-subject variability was determined assuming that individual parameters followed a multivariate lognormal distribution. Lag time (Tlag) was used to model the absorption process. Several covariates were tested, including age, sex, weight, and body mass index (BMI). Based on the results, the data was best described by the pharmacokinetic model with a first-order absorption rate constant (Ka, fraction F1), and a simultaneous first order absorption rate constant (Ka2, fraction 1-F1) with a lag time (Tlag 2) and first-order elimination (Table V). BMI was the only significant covariate, with an improvement in the individual goodness-of-fit plot performance. Figure 3 shows the visual predictive check of this double absorption model. Through population modeling, we characterized a subpopulation comprising 22% of the total population with different absorption rates and a delay time for the second absorption peak. These data are consistent with those observed previously and could result from issues related to the bioavailability of the drug (Castro *et al*., 2009). The results also indicated that the model continues to show high coefficients in the relative standard error of the parameters, suggesting that other covariates should be integrated into the model to explain the variability observed in the absorption phase. Despite the limited plasmatic data available for the model adjustment, it was determined that an association between the dissolution release profile and the *in vivo* data was not identified mainly due to the wide variability in albendazole absorption.

TABLE V - Parameter estimates of the final albendazole population model from 12 volunteers

	Parameter estimate (RSE [%])	
Fixed effect parameter	**Base model**	**Final model**
Ka1 (h-1)	0.4 (54)	1.45 (41.7)
Ka2 (h-1)	0.005 (103)	0.3 (59.4)
F1	0.18 (44.8)	0.22 (31.2)
Tlag2		0.58 (46.3)
V/F (L)	1.86 (87)	4.43 (54.1)
Cl/ F (L/h) β_BMI_CL/F	2.45 (52.1)	10.11 (53.9) 1.75 (42.1)

TABLE V - Parameter estimates of the final albendazole population model from 12 volunteers

Random Effects parameters		
ω_Ka1	0.75 (59.9)	0.2 (66.4)
ω_Ka2	1.94 (38.3)	1.44 (67)
ω_F1	0.24 (298)	0.63 (87.4)
ω_Tlag2		0.94 (34)
ω_V/F	0.75 (85.6)	0.97 (47.7)
ω_Cl/F	0.99 (32.8)	0.37 (22.9)
Error model		
Additive	1.64 (15)	1.62 (11.3)
Proportional	0.51 (8.7)	0.41 (8.19)
BIC	1634.07	1587.48
-2LL	1596.01	1508.03
AIC	1620.01	1558.03

ka- Absorption rate constant; CL/F- Apparent clearance; V/F- Apparent volume of distribution; Tlag- Lag time; SE- Standard error; ω- Between subject variability; b- The estimated effect of the covariate; RSE- Relative standard error; 2LL- 2 log-likelihood; BIC- Bayesian information criterion; AIC- Akaike information criterion

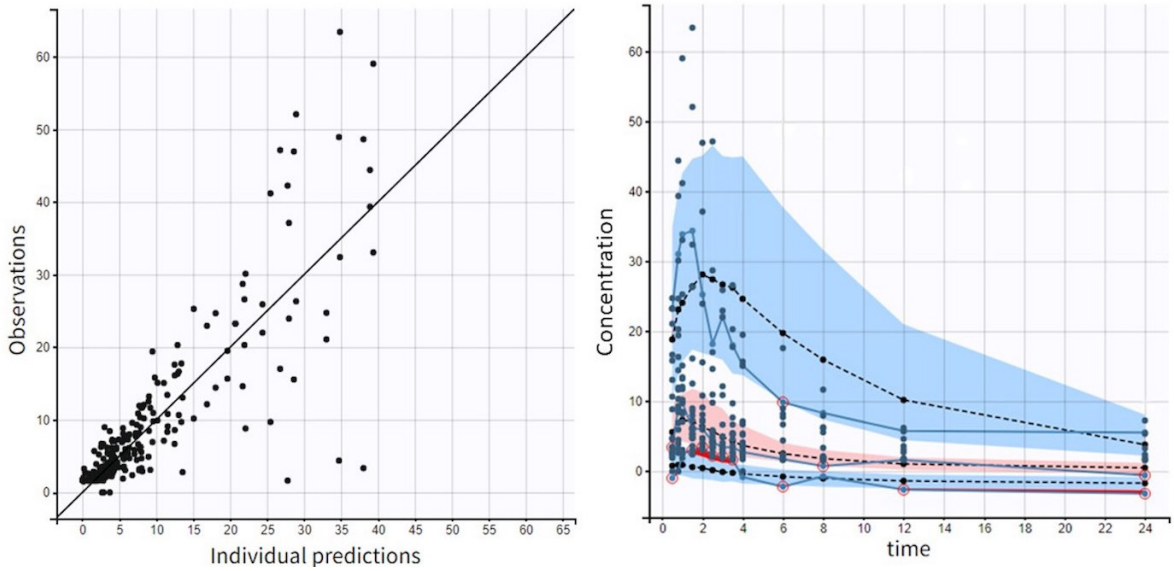

FIGURE 3 – Visual predictive check (VPC) of model building with shaded areas representing the prediction interval at the 5th, 50th and 95th of simulated concentrations generated from the final model (1000 replicates) and observed data (points) for albendazole.

CONCLUSIONS

The results of this study indicate that although the generic products containing albendazole met the quality control test specifications according to the Mexican Pharmacopoeia, these products showed differences in their respective dissolution profiles to those of the reference product. The *in vivo* pharmacokinetic study

showed wide intra- and interindividual variability in the plasma levels of albendazole and albendazole sulfoxide; therefore, no significant differences in the pharmacokinetic parameters C_{max} and AUC for the test and reference products were found.

The nonlinear mixed-effects modeling showed that the pharmacokinetics of ALB was best described by a two absorption peaks model, which could be associated with differences in the absorption process in the study population.

Our results showed that the *in vitro* pharmacopeial conditions for the albendazole dissolution test could be used for routine and in-process quality control, but due to the high variability in albendazole absorption, it would not be representative of the *in vivo* properties of the drug.

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