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Albendazole sulphoxide kinetic disposition after treatment with different formulations in dogs

A. DIB*
S. PALMA†,‡
G. SUÁREZ*
C. FARÍAS‡,§
P. CABRERA§
S. CASTRO†,‡
D. ALLEMANDI†,‡
L. MORENO‡,¶
C. LANUSSE‡,¶ &
S. SÁNCHEZ BRUNI‡,¶

**Laboratory of Pharmacology, Faculty of Veterinary Medicine- Universidad de la República, Uruguay; †Laboratory of Pharmaceutical Technology, Department of Pharmacy, Faculty of Chemical Sciences, Universidad Nacional de Córdoba, Argentina; ‡Consejo Nacional de Investigaciones Científicas y Tecnológicas (CONICET)-Argentina; §Department of Parasitology and Parasitological Diseases, Faculty of Veterinary Medicine-Universidad de la República, Uruguay; ¶Laboratory of Pharmacology, Faculty of Veterinary Medicine, Universidad Nacional del Centro, Argentina*

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New therapeutic strategies based on the search of alternative formulations of albendazole (ABZ) and albendazole sulphoxide (ABZSO) are under current development to optimize posology and antiparasite efficacy in dogs. In an incomplete block design, nine dogs were randomly divided into three groups ($n = 6$). Treatments were carried out in two phases as follows. Phase I: *Group I (treatment A),* animals received ABZ at 25 mg/kg of conventional formulation. *Group II (treatment B), dogs* received 25 mg/kg of a modified poloxamer-ABZ formulation. *Group III (treatment C),* animals were treated with ABZSO in equimolar amount to ABZ doses. After 21 days of wash-out period the experiment was repeated (Phase II). Blood samples were collected over 24 h and subsequently analysed by high performance liquid chromatography. ABZSO and $ABZSO_2$ were the analytes recovered in plasma. Significant higher *($P < 0.001$)* ABZSO area under the concentration–time curve (+500%) and C_{max} (+487%) values were obtained for the treatment C in comparison with treatments A and B. However, no statistical differences on pharmacokinetic parameters were found between formulations A and B. In conclusion, the enhanced plasma concentration profile obtained for the ABZSO formulation used in treatment C may contribute to optimize the anthelmintic control in dogs.

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Professor S. F. Sánchez Bruni, Laboratory of Pharmacology, Faculty of Veterinary Medicine, Universidad Nacional del Centro de la Provincia de Buenos Aires, Campus Universitario-7000-Tandil-Argentina. E-mail: ssanchez@vet.unicen.edu.ar

INTRODUCTION

Internal parasitic diseases in small animals are relevant in clinical practice. The treatment and control of helminth parasites require epidemiological knowledge of the parasite involved and understanding of the pharmacological features of the anthelmintic drugs available in the market. Benzimidazole (BZD) methyl-carbamate compounds are used to treat parasitic diseases in humans and domestic animals worldwide. For a variety of compounds, physical and chemical interactions, dilution effects and/or pH modifications in pharmaceutical formulations in different body compartments may affect their absorption and tissue distribution. BZD compounds are all relatively insoluble in water, benzene and ether, but highly soluble in alcohol and nonpolar solvents (Towsend & Wise, 1990). The latter limits the practical use of the most potent BZD compounds, including fenbendazole (FBZ), oxfendazole (OFZ) and albendazole (ABZ), to suspensions, which are most commonly administered by the oral route in domestic animals. ABZ is a BZD methylcarbamate anthelmintic compound effective against lungworms and gastrointestinal (GI) nematodes, tapeworms and liver flukes (Campbell, 1990; McKellar & Scott, 1990). The intrinsic anthelmintic action of BZD compounds on the parasite relies on a progressive disruption of basic cell functions as a result of their binding to parasite tubulin and depolimerization of microtubules (Lacey, 1990). ABZ, FBZ and OFZ, which is FBZ sulphoxide, mebendazole and the pro-drug Febantel, are the traditional compounds commonly used in small animals. However, a new BZD compound namely albendazole sulphoxide (ABZSO) or ricobendazole is available in the veterinary market of some South American countries. This is the active metabolite of ABZ formed by flavin monooxygenase–mediated sulphonation process (Fig. 1).

In vivo studies have demonstrated that the oral absorption of BZD compounds depends on their dissolution at low pH and is closely related to the rate of gastric emptying and gut transit

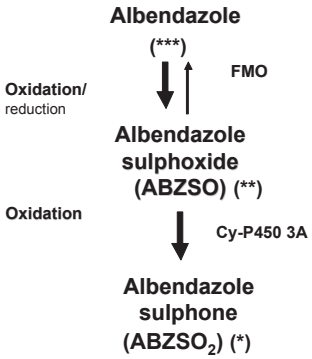

Fig. 1. Proposed metabolic pathway for albendazole and metabolites. Oxidation processes are mediated by flavine monooxygenase (FMO) and cytochrome-P450 (CY-P450 3A). The anthelmintic potency of parent drug and metabolites is represented as: (NA) no activity, (*) very poor or no activity, (**) good activity, (***) very good activity. *Adapted from Sánchez Bruni et al., 2006.*

time (Lanusse et al., 1993; Sánchez Bruni et al., 1999). Fasting dietary composition and formulation differences have all been shown to affect the pharmacokinetic (PK) behaviour and resultant efficacy of BZD compounds in mammals. A rich fatty diet improves ABZ absorption in humans (Edwards & Breckenridge, 1988), although the same effect was not observed in dogs fed with high-fat diets (McKellar et al., 1993). However, ABZ has consistently been shown to be better absorbed than lipidic matrix formulations in both dogs (Sánchez Bruni et al., 2000) and humans (Savio et al., 1998). Pharmaceutical formulations of BZD molecules, which increase their bioavailability or extend their residence times in monogastrics, could improve their anthelmintic efficacy. A matrix with poloxamer was developed as one of ABZ-based formulation in this study. The poloxamer polyols are a series of closely related block copolymers of ethylene oxide and propylene oxide conforming to the general formula HO (C2H4O)a(C3H6O)b(C2H4O)a H. These have been widely used as wetting and solubilizing agents and surface adsorption excipients. The polyoxyethylene segment is hydrophilic, while the polyoxypropylene segment is hydrophobic. All of the poloxamers are chemically similar in composition, differing only in the relative amounts of propylene and ethylene oxides added during manufacture. Poloxamers are not metabolized in the body and are used in a variety of oral, parenteral and topical pharmaceutical formulations, generally regarded as nontoxic and nonirritant materials. Poloxamer 188 (P 188) was also used as meltable solid binder in some new pharmaceutical particles attainment techniques as fluidized hot melt granulation and melt agglomeration process. This potential carrier present a low melting point (about 52–57 °C), surfactant properties and oral safety (Collett & Popli, 2000; Vilhelmsen, 2005; Zhai, 2008). In vitro dissolution rate assays of ABZ undertaken at our laboratory showed a significant increase on ABZ dissolution using P188 as carrier in solid dispersions or physical mixtures.

The need to identify alternative ABZ-mediated anthelmintic preparations for use in companion animals motivated the development of the trial described here.

The aim of the current work was to describe the kinetic behaviour of ABZ-related metabolites after the administration of different pharmacotechnical preparations. Assessment of the systemic availability of active drug/metabolites will contribute to identify drug formulation for clinical use.

MATERIALS AND METHODS

Animals

Nine (n = 9) crossbreed dogs (2–4 years old), one male and eight nonpregnant females (41 ± 1.87 kg), were involved in this trial (Uruguayan Navy Force military working dogs). All animals were GI parasites-free demonstrated by two consecutive faecal egg counts reduction test. All animals had free access to water, were fed with balanced food and were in good health as determined by physical examination before the administration of drugs. Animal procedures and management protocols were approved by the Ethics Committee according to the Animal Welfare Policy of the Faculty of Veterinary Medicine, Universidad de la República, Montevideo, Uruguay. (http://www.fvet.edu.uy).

Chemicals

Formulation of ABZ was prepared by weighing 200 mg of pure drug and transferred into a gelatin hard capsule. Modified formulation of ABZ with poloxamer (1:1) was prepared by adding the drug to the molted carrier (at 63 °C) in a water bath. The mixtures were stirred, and the resulting homogenous preparations rapidly cooled. Subsequently, the dispersions were pulverized; a 212-micron particle size fraction was obtained by sieving and kept in a screw-capped glass vial, until its placement in a hard gelatin capsule. Each filled capsule contained a concentration equivalent to 200 mg of ABZ. The formulation based in ABZSO was purchased by Afford, Argentina. Standards of ABZ, ABZ-sulphoxide (ABZSO), ABZ-sulphone ($ABZSO_2$) and oxibendazole (OBZ) were used for the analytical analysis of samples.

Experimental design

Experimental dogs were randomly allocated into three groups (n = 3) (Group I: animal #1, #2, #3; Group II: animal #4, #5, #6; Group III: animal # 7, #8, #9) and received three different treatments using an incomplete blocking design.

Each experimental treatment was given to six animals in two phases: Phase I: animals in Group I received ABZ at 25 mg/kg as a conventional formulation (capsules) (treatment A). Animals in Group II received 25 mg/kg of a modified poloxamer-ABZ formulation (treatment B) and dogs belonging to Group III were treated with ABZSO in a dosage equimolar to that of ABZ (treatment C). After 21 days of wash-out period, the treatments were repeated as Phase II: Group I received treatment B, Group II received treatment C and Group III received treatment A.

Blood samples

Blood samples were taken prior to and following treatments and were collected from the saphene vein using a 18 G catheter before administration (time 0) and at 0.25, 0.5, 1, 2, 4, 8, 12, 18 and 24 h after the oral treatments and immediately transferred into heparinized tubes. Plasma was separated by centrifugation at 3000 ***g*** for about 15 min, placed into plastic tubes and frozen at −20 °C until analysis by high performance liquid chromatography (HPLC).

Analytical procedures

ABZ metabolites analysis. Sample clean up: ABZ, ABZSO and $AZBSO_2$ were extracted using disposable C18 columns. Ten microlitres of OBZ (50 μg/mL) was added to 500 μL of plasma in a glass test tube. Spiked samples were placed into a C18 column preconditioned with 0.5 mL of methanol (Mallinekradt Chemicals) followed by 0.5 mL water, in a vacuum system. Samples were washed (2 mL of water) and then eluted with 2 mL of HPLC-grade methanol. After elution, all samples were concentrated to dryness in a vacuum concentrator and then reconstituted with 200 μL of mobile phase.

HPLC analysis: Experimental and spiked plasma samples (used for validation) were analysed by HPLC with a UV detector. Fifty (50) microlitres of each previously extracted sample was injected and the analytes eluted (flow 1.2 mL/min) from the analytical column (5 μm, 250 mm × 4.6 mm, C18 column), using a linear gradient method as reported by Sanchez *et al.*, (1996). The compounds were identified by the retention times of pure reference standards. Plasma calibration curves for each analyte were constructed by least squares linear regression analysis giving a correlation coefficient (r) between 0.9987 and 0.9995. Quantification limits were 0.01 μg/mL (ABZ and ABZSO) and 0.03 μg/mL ($ABZSO_2$).

Pharmacokinetic analysis of the data. The concentration vs. time curves for the metabolites ABZSO and $ABZSO_2$ in plasma for each individual animal after the different treatments were fitted with PK Solution 2.0 (Summit research services, Ashland, OH, USA). The following equation (Notari, 1987) was used to describe the biexponential concentration–time curves for ABZSO and $ABZSO_2$ after the oral treatment:

$$Cp = Be^{-\lambda 2t} - Be^{-\lambda 1t}$$

where: Cp = concentration in plasma at time t after administration (μg/mL); B = concentration at time zero extrapolated from the elimination phase (μg/mL); e = base of the natural logarithm; λ_2 = terminal slope (h^{-1}); and λ_1 is the slope obtained by feathering, which represents either the first-order absorption rate constant (λ_1) or first-order metabolite formation rate constant (λ_{for}) (h^{-1}). The elimination half-life ($t_{1/2}\lambda_2$) and absorption ($t_{1/2}\lambda_1$) or metabolite formation half-lives ($t_{1/2}\lambda_{for}$) were calculated as $ln2/\lambda_2$ and $ln2/\lambda_1$, respectively. The peak concentration (C_{max}) and time to peak concentration (T_{max}) were displayed from the plotted concentration–time curve of each analyte. The area under the concentration–time curve (AUC) and area under the first moment curve (AUMC) were calculated by the linear trapezoidal rule (Gibaldi & Perrier, 1982).

$$AUMC_{(0-t)} = \sum_{i=0}^{n-1} \frac{t_{i+1} - t_i}{2}(C_i t_i + C_{i+1} t_{i+1}) + \frac{C_{last} \cdot t_{last}}{\lambda_z} + \frac{C_{last}}{\lambda_z^2}$$

The mean residence time was determined as AUMC/AUC.

Statistical analysis of the data: The ANOVA test was used for the multiple statistical comparisons of the PK data obtained from the different groups. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Albendazole parent drug was not detected in plasma after the three treatments assayed. ABZSO was detected in plasma for 12 h (treatment A) and 24 h (treatments B and C). The comparative plasma PK curves after the oral administration of the three different formulations for ABZSO are shown in Fig. 2. Table 1 summarizes plasma PK parameters of ABZSO and $ABZSO_2$ obtained after oral administration for the three different formulations. The ABZSO plasma disposition after the administration of ABZSO (treatment C) was greater ($P < 0.01$) compared with those obtained for treatments A and B.

The observed AUC values $_{(0\text{-}LOQ)}$ were 87% (treatment A) and 97% (treatment C) of those AUC values estimated after extrapolation to infinity ($_{0-\infty}$) (Table 1).This ratio seems to indicate that extrapolation to infinity accounts for a low percentage within the total AUC estimation. However, the situation could be slightly different for formulation used in treatment B (78%) where more data-point obtained on the elimination phase may

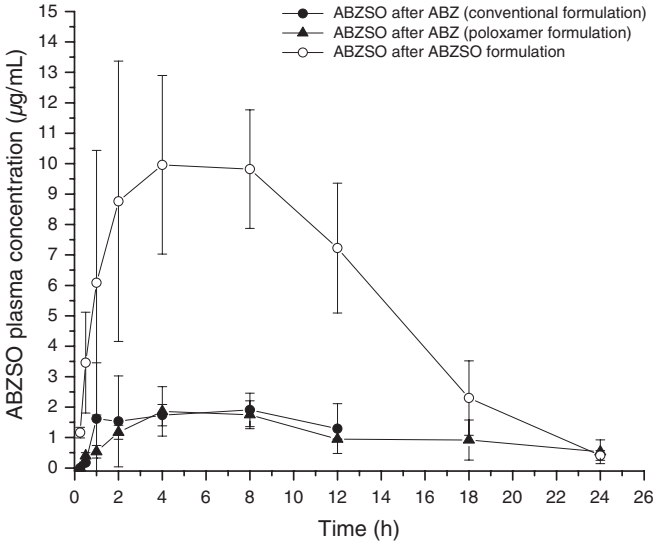

Fig. 2. Comparative (mean ± SD) plasma profiles (n = 6) for albendazole sulphoxide (ABZSO) after the administration of three different oral-based albendazole (ABZ) and derivative formulations.

Table 1. Comparative plasma disposition kinetic variables for albendazole sulphoxide (ABZSO) and albendazole sulphone ($ABZSO_2$) after the oral administration of three different formulations

	GROUP 1 ABZ Control (Capsules)		GROUP 2 ABZ-poloxamer (Capsules)		GROUP 3 ABZSO (Tablets)	
Pk parameters	ABZSO	$ABZSO_2$	ABZSO	$ABZSO_2$	ABZSO	$ABZSO_2$
C_{max} (μg/mL)	2.42 ± 1.26^a	0.42 ± 0.32^a	1.92 ± 1.44^a	0,31 ± 0.26^a	11.7 ± 3.13^b	1.74 ± 0.22^b
T_{max} (h)	5.34 ± 2.54^a	10.3 ± 3.47^a	3.12 ± 2.76^a	15.2 ± 8.44^a	7.26 ± 3.53^a	11.4 ± 4.76^a
$T_{½}$ λ_1 (h)	2.15 ± 1.32^a	2.74 ± 1.98^a	1.52 ± 1.12^a	3.12 ± 2.46^a	1.73 ± 0.75^a	1.54 ± 0.50^a
AUC $_{(0\text{-LOQ})}$ μg·h/mL)	18.1 ± 7.26^{a*}	2.93 ± 1.53^a	16.9 ± 9.85^{a*}	3.11 ± 2.61^a	136 ± 27.0^{b*}	23.5 ± 4.83^b
AUC $_{(0-\infty)}$ μg·h/mL)	20.7 ± 7.68^a	4.10 ± 1.22^a	21.6 ± 9.00^a	7.33 ± 2.93^a	140 ± 34.0^b	28.0 ± 10.2^b
AUC ratio $_{(0\text{-LOQ})}/_{(0-\infty)}$	0.87	–	0.78	–	0.97	–
AUMC total (μg·h^2/mL)	184 ± 92.0^a	56.7 ± 27.6^a	394 ± 167^a	39.4 ± 20.2^a	1237 ± 390^b	469 ± 140^b
$T_{½}$ λ_2 (h)	2.14 ± 1.38^a	2.83 ± 2.05^a	5.93 ± 2.93^a	2.34 ± 0.54^a	3.14 ± 1.52^a	2.92 ± 1.17^a
MRT (h)	8.24 ± 3.46^a	11.7 ± 7.23^a	16.2 ± 6.28^a	20.6 ± 7.50^a	8.73 ± 1.29^a	15.2 ± 5.29^a
PDP (h)	0.25–18	1.0–18	0.5–18	2.0–12	0.25–24	0.25–24

Different Superscript letters indicate statistical differences among groups at $P < 0.05$. $T_{½}$ λ_1, metabolite formation half-life; C_{max}, peak concentration; T_{max}, time at C_{max}; $AUC_{0\text{-LOQ}}$, area under the concentration vs. time curve observed from 0 to limit of quantification (LOQ) $AUC_{0-\infty}$, area under the concentration vs. time curve extrapolated to infinity; AUMC, area under the first moment concentration vs. time curve; $T_{½}$ λ_2, elimination half time; MRT, mean residence time; PDP, plasma detection period; NA, not applicable. *AUC values normalized by the dose.

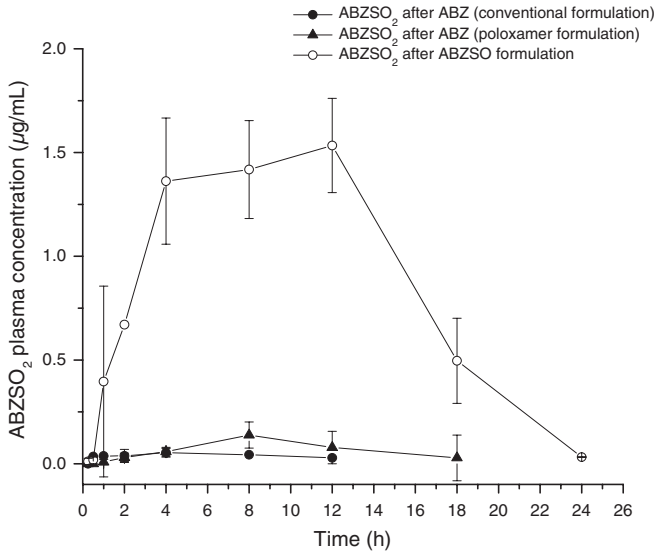

Fig. 3. Comparative pharmacokinetic profile (Mean ± SD) ($n = 6$) of albendazole sulphone ($ABZSO_2$) obtained after the oral administration of three different oral-based albendazole (ABZ) and derivative formulations.

have been necessary for a better characterization of the total AUC value.

The PK dispositions of $ABZSO_2$ (inactive metabolite) after given the three assayed formulations are shown in Fig. 3.

DISCUSSION

The pharmacological effects of a drug can generally be observed by a short time after its administration. However, between the administration and the pharmacological effect, the drug must cross rapidly or slowly biological barriers depending of the physical–chemical properties of the molecule given and the nature of the biological barrier (Sánchez Bruni *et al.*, 2006). The low aqueous solubility of BZD (pk = 7.8) may limit absorption during GI transit (McKellar & Scott, 1990; McKellar *et al.*, 1990), and this may be compounded by the short gut transit time of the dog compared to other domestic species (McKellar *et al.*, 1993). The rate of dissolution of BZD anthelmintics in the stomach of different animal species is thought to be extremely important in achieving adequate absorption, consequent availability, retrograde GI secretion and a high clinical efficacy.

Albendazole sulphoxide plasma concentrations (treatment C) were greater than the traditional albendazole and albendazole-poloxamer (P-188) formulations used in treatments A and B (Fig. 2). BZD compounds, such as ABZ formulated as suspension, capsules or tablets, must dissolve at low pH (stomach), and it has been demonstrated that the dissolution rate may be influenced by the particle size in the formulation (Hennessy, 1993) and also limited by the length and GI transit time (Sánchez Bruni *et al.*, 2006). Subsequently, the dissolved drug is absorbed, distributed through the body, metabolized and eventually eliminated.

The comparative PK study reported here shows significant increased values of AUC *($P < 0.001$)* (+500%) and C_{max} (+487%) for ABZSO after treatment C, when it was statistically compared with the other both treatments, 'A' and 'B', after a single oral dose.

When ABZSO was given as a single dose in tablets (treatment C), ABZSO (active metabolite) and $ABZSO_2$ (inactive metabolite) were the main metabolites detected in plasma upon 24 h post treatment (Table 1).

After treatment C, a higher ABZSO peak and concentration levels were measured on the systemic blood circulation, compared with the profile obtained after the administration of traditional ABZ (treatment A) and ABZ-poloxamer (treatment B).

The increased systemic concentrations are related with the physical and chemical properties of ABZSO metabolite, when it is compared with its parent drug ABZ (treatment A). The ABZSO plasma concentrations observed after treatment C resulted in + 500% higher than those obtained after the oral administration of the other two formulations assayed. It has been described that the aqueous solubility of ABZ is circa 0.01 mg/ml (Reppas *et al.*, 1999), while for ABZSO is approximately sixfold higher (Zimei *et al.*, 2005). This clearly shows a higher correlation between the solubility/dissolution of the compounds and the obtained AUC. For this reason, these results are also attractive for the subsequent design for oral modified release formulations.

On the other hand, the obtained results upon *in vitro* dissolution experiment, for using the addition of Poloxamer P188 as carrier in solid dispersion to improve the ABZ dissolution properties, did not correlate with a marked improvement of the plasma concentrations after given *in vivo* the formulation used in treatment B. The latter may be attributed to an increase in the dissolution surface area, in combination with improved wetability and ABZ solubilization as consequence of the carrier dissolution. However, works characterizing the gelation mechanism of poloxamer solutions have been carried out, indicating that when the solid dispersions are placed in water at 37° gel formation is expected (Ritger & Peppas, 1987; Peppas & Sahlin, 1989).

Outcome obtained in this *in vivo* trial suggested that treatment B had no significant variation on PK parameters when it was statistically compared with the parent drug formulated as conventional pharmaceutical formulation (treatment A). This is particularly likely in dogs owing to the short transit time in the GI tract (Plaza Carrión, 1995) compared to humans (Ganong, 1995). Hence, in dogs, the ABZ–poloxamer combination may pass through the more absorptive portion of the small intestine prior to complete dissolution and release of all drug molecules. Solid dispersion technology may be applied to increase the dissolution rate of highly lipophilic drugs thereby improving their bioavailability (Zerrouk *et al.*, 2001).

Usually in *in vitro* experiments, the dispersions are placed on the surface of the dissolution medium. However, in this *in vivo* study, dispersions were placed in capsules and this might have increased the 'gel formation' effect. Taking into account the results observed in this trial, the compaction and disintegration effects are currently being studied and experiments aimed at evaluating the feasibility of designing rapid disintegration tablets or capsules should be conducted (Chandrasekhar *et al.*, 2009; Srinarong *et al.*, 2009).

The experimental formulation used in treatment C has shown a high antiparasite efficacy. Plasma profiles of treatment 'C' correlate with its great efficacy (>90%), with a single dose against the most pathogenic nematodes (larval and adult stages), giving at least 30 days of protection period (Saumell *et al.*, 2006).

Pharmacokinetic profile data of the experimental ABZSO formulated as oral tablets (treatment C) could contribute to evaluate its high potential as an anthelmintic drug single dose for GI parasite control in dogs as well as in the future to be proved in humans. The outcome of the work described here would contribute to identify anthelmintic formulations with improved absorptions pattern and systemic availability to use in companion animals. An adequate understanding of the active drug kinetic behaviour is pivotal to optimize drug efficacy against adult and larval stages of different helminth parasites.

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