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ORIGINAL ARTICLE

# Pharmacokinetics and milk excretion pattern of eprinomectin at different dose rates in dairy cattle

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## Abstract

This study aimed at determining the plasma disposition kinetics of eprinomectin (EPM) and EPM excretion pattern through milk after topical administration to dairy cattle at the recommended dose of 0.5 mg/kg and at 1 and 1.5 mg/kg. A high variability in the plasma concentration profiles was observed among animals, particularly in the Cmax values, with a coefficient of variation between 39 and 53%. The Cmax and AUC values were significantly affected by the dose administered at 1.5 mg/kg. However, such differences did not seem to follow a linear pattern among treatments. These parameters did not differ among dose rates after dose normalization; nevertheless, the simulation of a linear kinetic disposition showed a mean plasma AUC value of 254 ng.d/ml instead of the observed value of 165 ng.d/ml. EPM concentration profiles in milk were significantly lower than those measured in plasma. The Cmax and AUC milk-to-plasma ratios ranged from 0.14 to 0.26 and 0.16 to 0.21, respectively ($p>0.05$). The low milk-to-plasma ratio of EPM accounted for a low percentage of the fraction of the administered dose excreted through milk, being significantly higher at a dose rate of 0.5 mg/kg (0.07%) of EPM than at 1.5 mg/kg (0.04%) ($p<0.05$). The topical administration of EPM to lactating dairy cows at higher doses than that recommended for gastrointestinal nematodes showed a milk excretion pattern with a zero milk withdrawal period. In conclusion, the administration of topical EPM formulation at 1 or 1.5 mg/kg may be a valuable tool to be used in regional strategic deworming programs aimed to control ectoparasite infections in dairy production systems.

**KEYWORDS**
dairy cattle, eprinomectin, macrocyclic lactones, milk excretion, pharmacokinetics

## 1 | INTRODUCTION

Parasite diseases cause productivity losses in dairy animals, with economic effects that can be reduced using anthelmintic therapy (Vercruysse & Claerebout, 2001). Despite their benefits, anthelmintics used in dairy cows cause public health and food safety concerns due to the unwanted presence of drug residues in milk (Imperiale et al., 2004; Tsiboukis et al., 2013). Macrocyclic lactones (MLs) are anthelmintic drugs with endo- and ectoparasiticidal activity (Campbell, 1983; Vercruysse & Rew, 2002). Overall, MLs are considered to have similar biological activity; however, differences in the chemical structure among MLs members account for specific pharmacokinetic (PK) and pharmacodynamic (PD) features (Lanusse, 1997). In addition, the ML structure also has a significant effect on the distribution rate between milk and plasma and, consequently, on the presence of drug residues in milk (McKellar & Gokbulut, 2012). This topic is an important factor influencing the selection of treatments to be applied in dairy animals, considering the importance

  

of reducing the withdrawal times of anthelmintic treatments (Nava et al., 2015).

Eprinomectin (EPM), an ML member, is an amino-avermectin derivative of avermectin $B_1$ analogues. EPM shows a similar broad-spectrum activity against nematodes and arthropods to that of the other MLs (Shoop et al., 2001; Williams et al., 1999). However, changes in the chemical structure of EPM determine a lower milk partitioning coefficient than that of other ML members (Shoop et al., 1996). The pioneer EPM formulation at 0.5% was topically administered to dairy cows and has the advantage of zero-day withdrawal in milk. For this reason, in Argentina, it is used for controlling ectoparasites, such as *Riphichephalus (Boophilus) microplus (R. (B.) microplus)*, which affect dairy cows in endemic areas. The administration regime of EPM is based on previous works that investigated the acaricidal activity and PK of EPM following different administration protocols for beef cattle. The efficacy of EPM against *R. (B.) microplus* was evaluated in a double application treatment regimen with a 4-day interval between treatments at 0.5 mg/kg (Davey & George, 2002) and in a single administration at 1 mg/kg (Aguirre et al., 2005). An integrated study on the PK and efficacy of EPM topically administered at doses 2 and 3 times (1 and 1.5 mg/kg) higher than the therapeutic dose was conducted (Lifschitz et al., 2016). However, there is no available information about the influence of EPM dose rate on the systemic exposure and drug residues in milk after the topical administration to dairy cattle. The present study evaluated the plasma disposition kinetics and the excretion pattern of EPM through milk after topical administration to dairy cattle at the recommended dose of 0.5 mg/kg and at 1 and 1.5 mg/kg.

## 2 | MATERIALS AND METHODS

### 2.1 | Experimental animals, treatment and sampling

Eighteen clinically healthy Holando Argentino cows in the late stage of lactation were used; their mean body weight was 622 ± 68 kg. The study was conducted in the dairy farm of the School of Agrarian Education N° 1 'Dr. Ramón Santamarina', located in Tandil, Argentina. Cows were milked twice a day using mechanical vacuum milking machines, and milk production was measured before the start of and throughout the trial. The average milk production during the experimental period was 23.5 ± 3.10 l/animal/day. The animal health status was monitored throughout the study. Dosages were calculated based on individual body weight, and the treatment was started after milking process was completed. Experimental animals were allocated to three experimental groups of six animals each and treated with a commercial formulation of eprinomectin (EPM) 0.5% solution (IVOMEC® EPRINEX® POUR ON, Merial Argentina S.A.) at 0.5 mg/kg (EPM 0.5mg/kg), 1 mg/kg (EPM 1mg/kg) and 1.5 mg/kg (EPM 1.5mg/kg). EPM solution was applied topically (pour-on) on day 0 directly on the skin along the back line from the withers to the tail head. The animal health status was monitored throughout the study. No adverse reactions were observed at the site of application after treatment. Blood samples were taken from the jugular vein into heparinized vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ) before and at 1, 2, 3, 5, 7, 9, 11, 15 and 21 days post-treatment. Plasma was separated by centrifugation at 2000 *g* for 20 min, and the recovered plasma was transferred into labelled vials. Milk samples were collected following the same plasma scheme. At each sampling time, a composite milk sample (50 ml, from the four udders) was collected by hand milking after discarding 30–50 ml and before the complete mechanical milking of each cow. Plasma and milk samples were stored at −20°C until processing.

## 3 | ANALYTICAL PROCEDURES

### 3.1 | Reagents

Pure reference standards of EPM and abamectin (ABM) were used to validate the high-performance liquid chromatography (HPLC) method. Standard solutions of EPM were prepared by successive dilutions in methanol from the parent stock solution (1 mg/ml) and stored at -18° C. A concentration of 10 ng of ABM, used as internal standard (IS), was added to both fortified and experimental samples. Acetonitrile and methanol solvents used during extraction and chromatographic analysis were HPLC grade and purchased from JT Baker® (Center Valley, PA, US). Water was double distilled and deionized using a water purification system (Simplicity®, Millipore, Sao Paulo, Brazil).

### 3.2 | Drug extraction, derivatization and chromatographic conditions

EPM and ABM were extracted from spiked and experimental samples (plasma and milk) following the methodology described by Imperiale et al. (2006). Briefly, a 0.25 ml-aliquot of plasma and 1 ml-aliquot of milk was combined with 10 ng of IS (ABM) mixed with 1 ml of acetonitrile. The solvent sample was mixed for 20 min and then centrifuged at 2000 *g* for 15 min. The supernatant was injected into a $C_{18}$ cartridge (Strata®, Phenomenex, CA, US), previously conditioned by passing 2 ml of methanol and 2 ml of deionized water. The cartridge was flushed with 1 ml of water followed by 1 ml of water/methanol (4:1, v/v). The compounds were eluted with 1.5 ml of methanol and concentrated to dryness under a nitrogen stream. Samples were subjected to derivatization, as described by Danaher et al. (2001). Once the reaction was completed, an aliquot (100 μl) of each sample was injected directly into the chromatographic system. Concentrations of EPM were determined using a Shimadzu LC-10ATVP HPLC system (Shimadzu Corporation, Kyoto, Japan), which included a fluorescence detector set at an excitation wavelength of 365 nm and an emission wavelength of 475 nm. The mobile phase of deionized water, methanol, triethylamine, phosphoric acid and acetonitrile (6:25:0.2:0.2:68.6,

v/v/v/v/v) was pumped at a flow rate of 1.0 ml/min through a $C_{18}$ reverse-phase column (5 m, 250 by 4.60 mm; Kromasil, Eka Chemicals, Bohus, Sweden) kept in an oven set at 30°C. EPM was identified by matching their retention times with those of pure reference standards. Chromatographic peak areas were determined using the integrator software (Class LC 10 Software, version 1.2, Shimadzu Corporation) of the HPLC system.

### 3.3 | Validation method

A complete validation of the analytical procedures for extraction and quantification of EPM from both plasma and milk was performed before analysing the experimental samples. Calibration curves were constructed in the range between 0.1 to 100 ng/ml (plasma) and 0.1 to 10 ng/ml (milk) and were established using least squares linear regression analysis. Correlation coefficients (*r*) and coefficient of variations (CV) were calculated. Linearity was established to determine the EPM concentrations/detector responses relationship. Percentages of EPM recovery from plasma and milk were >70%. The precision of the extraction and chromatography procedures for plasma and milk samples was estimated by processing replicate aliquots (*n*= 4) of samples containing known EPM concentrations. The precision showed a coefficient of variation <5% for both matrices. The limit of quantification was established at 0.1 ng/ml for both set of samples.

### 3.4 | Pharmacokinetics and statistical analysis of the data

The plasma and milk concentration *vs*. time curves obtained after treatment of each individual animal were fitted with the PK Solutions 2.0 (Ashland, OH, US) computer software. PK parameters were determined by the non-compartmental analysis. The peak plasma concentration (Cmax) was obtained from the plotted plasma concentration-time curve of each individual animal. The area under the concentration-versus-time curves (AUC) was calculated by the trapezoidal rule (Gibaldi & Perrier, 1982) and further extrapolated to infinity. The terminal (elimination) half-life ($T_{1/2}$el) was calculated as In2/$\lambda_z$, where In2 is the natural logarithm of 2 and $\lambda_z$, the slope of the terminal phase. The $\lambda_z$ was determined by performing regression analysis using at least four points of the terminal phase of the concentration-time plot. The percentage of drug elimination through milk was calculated using the following equation:

$$\%\ \text{dose excreted through milk} = (V_{\text{milk}} \times C_{\text{milk}}/D) \times 100.$$

where $V_{milk}$ is the individual milk production (ml); $C_{milk}$ is the drug concentration in milk (ng/ml), and *D* is the total administered dose (mg).

The plasma exposure after EPM administration at 1 and 1.5 mg/kg was simulated based on the calculation of a linear kinetic disposition of both doses after the administration at 0.5 mg/kg using PCModfit 6.9 software (Allen, 1990). The estimated values were compared to those observed after EPM quantification in plasma for each dose rate.

Plasma and milk concentrations of EPM and all the PK parameters are reported as mean ±SD. Mean PK parameters were statistically compared using one-way ANOVA. The assumption of equal variance of the data obtained after treatments was assessed using a non-parametric Kruskal–Wallis test, which showed significant differences among standard deviations. A similar procedure was used to compare drug concentrations measured in plasma and milk. The statistical analysis was performed using Instat 3.0 Software (Graph Pad Software, CA, US). A value of $p<0.05$ was considered statistically significant.

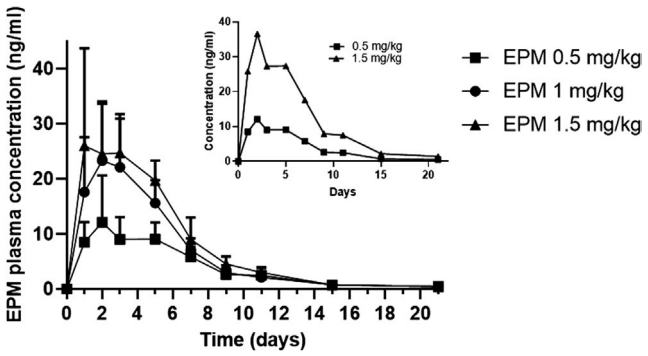


**FIGURE 1** Comparative (mean ±SD, *n*=6 per group) plasma concentration profiles (ng/ml) of eprinomectin (EPM) obtained after topical (pour-on) administration to dairy cows at 0.5, 1 and 1.5 mg/kg. The insert shows the mean simulated concentrations obtained after the 0.5 and 1.5 mg/kg doses based on a linear kinetic disposition calculation

## 4 | RESULTS

EPM plasma concentrations in dairy cows were measured from day 1 of topical administration at 0.5, 1 and 1.5 mg/kg, and during the whole sampling period up to 21 days. The plasma concentrations *vs*. time profiles of EPM obtained for each treatment are plotted in Figure 1. Disposition kinetics of EPM was characterized by a slow absorption up to maximal concentrations reached between 2.17 and 3 days post-administration, followed by a progressive decrease of drug concentrations until comparable levels among groups were reached, about 9 days post-treatment. There were not significant differences among Tmax values in plasma after the administration of the different doses. EPM was detected in plasma until day 21. A high variability in the plasma concentrations profiles was observed among animals, particularly in Cmax, which had a coefficient of variation between 39 and 53%. A summary of the main plasma PK parameters for the different dose regimens is presented in Table 1. The Cmax and AUC values were significantly affected by the dose administered only for 1.5 mg/kg. However, such differences did not seem to follow a linear pattern among treatments. After dose normalization, these parameters did

| Kinetic parameters | EPM 0.5 mg/kg | EPM 1 mg/kg | EPM 1.5 mg/kg | *Pvalue* |
|---|---|---|---|---|
| Tmax (days) | 2.67 ± 1.86[a] | 3.00 ± 1.10[a] | 2.17 ± 1.60[a] | 0.637 |
| Cmax (ng/ml) | 14.1 ± 7.49[a] | 24.6 ± 9.59[ab] | 30.7 ± 13.9[b] | 0.047 |
| $AUC_{0\text{-}21d}$ (ng.d/ml) | 80.0 ± 15.3[a] | 136 ± 50.9[ab] | 165 ± 44.7[b] | 0.007 |
| $T_{1/2}$el (days) | 3.34 ± 1.08[a] | 2.47 ± 0.47[a] | 2.67 ± 0.49[a] | 0.134 |
| MRT (days) | 5.93 ± 1.37[a] | 4.62 ± 0.38[a] | 4.77 ± 0.68[a] | 0.072 |
| *Normalized Cmax | 14.1 ± 7.49[a] | 12.3 ± 4.79[a] | 10.2 ± 4.62[a] | 0.534 |
| *Normalized AUC | 80.0 ± 15.3[a] | 67.8 ± 25.4[a] | 54.8 ± 14.9[a] | 0.108 |

**TABLE 1** Pharmacokinetic parameters (mean ±SD, *n*=6 per group) for eprinomectin (EPM) in plasma after topical administration to dairy cows at 0.5, 1 and 1.5 mg/kg

*Note:* Different letters indicate statistical differences at $p<0.05$.

Abbreviations: $AUC_{0\text{-}21d}$, area under the concentration *vs*. time curve from time zero to 21 days post-administration; Cmax, peak plasma concentration; MRT, mean residence time; $T_{½}$el, elimination half-life; Tmax, time to peak plasma concentration.

*Cmax and AUC values were dose-normalized by dividing the obtained values by 2 (EPM 1mg/kg) and 3 (EPM 1.5mg/kg).

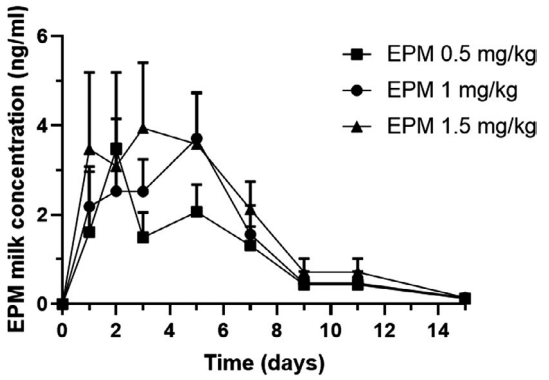


**FIGURE 2** Comparative (mean ±SD, *n*=6 per group) milk concentration profiles (ng/ml) of eprinomectin (EPM) obtained after topical (pour-on) administration to dairy cows at 0.5, 1 and 1.5 mg/kg

not differ among the different dose rates; nevertheless, the simulation of a linear kinetic disposition showed a mean plasma AUC value of 254 ng.d/ml instead of the observed value of 165 ng.d/ml.

In all experimental animals, EPM was detected in milk until day 15 post-administration. The milk concentration profiles of EPM after topical administration at different dose rates are shown in Figure 2. Milk concentrations of EPM were significantly lower than those measured in plasma. Tmax in milk was significantly delayed after the administration of 1 mg/kg compared to the other two doses. Table 2 shows the comparative PK parameters for EPM in milk for each experimental group. The Cmax and AUC milk-to-plasma ratios ranged from 0.14 to 0.26 and 0.16 to 0.21, respectively, without differences among experimental groups (Figure 3). There was a significant correlation between Tmax values in plasma and those achieved in milk ($r$ 0.52, $p$ 0.02). The low milk-to-plasma ratio of EPM accounted for a low percentage of the fraction of administered dose excreted in milk. This fraction was significantly higher when EPM was administered at 0.5 mg/kg (0.07%) than at 1.5 mg /kg (0.04%) ($p<0.05$). EPM concentrations in milk were below the maximum residue limit (20 ng/mL) throughout the whole sampling period after its administration at the three dose rates tested.

## 5 | DISCUSSION

Successful management of anthelmintic drugs requires integration of pharmacological, parasitological and epidemiological knowledge. Topical administration of ML shows advantages and disadvantages in the different cattle production systems. These commercial formulations should be easy to deliver and reduce stressful conditions of animals. However, physio-pharmacological factors, such as breed, body composition and licking behaviour, may trigger a highly variable pharmacokinetic and pharmacodynamic response (Laffont et al., 2001; Sallovitz et al., 2002; Toutain et al., 2012). The high variability in the efficacy against gastrointestinal nematodes after topical administration of ML was clearly corroborated by Leathwick and Miller (2013). In the current trial, the variability in the Cmax and Tmax of EPM in plasma was between 36 and 74% after administration at the three dose rates. Whereas the EPM Tmax values were similar in plasma after the administration of the three doses, a significant delayed Tmax was measured in milk after the administration of 1 mg/kg (Table 2). It seems that this result does not have a physio-pharmacological relevance. EPM milk concentrations remained at very low and constant levels during the first days after treatment and small variations may determine that the Cmax was achieved on day 2, 3 or 5.

Since injectable MLs are not approved for use in lactating dairy cows, EPM is considered a first-line treatment option because it has a zero-day milk withdrawal period. The impact of gastrointestinal parasitism on adult dairy cows has been studied over many years. Since the distribution of gastrointestinal nematodes in adult dairy cows is over-dispersed, the negative impact on milk production may be variable and a targeted selective treatment is recommended (Ravinet et al., 2014). The situation is quite different for dairy farms

**TABLE 2** Representative pharmacokinetic parameters (mean ±SD, *n*=6 per group) for eprinomectin (EPM) in milk after topical administration to dairy cows at 0.5, 1 and 1.5 mg/kg

| Kinetic parameters | EPM 0.5 mg/kg | EPM 1 mg/kg | EPM 1.5 mg/kg | *Pvalue* |
|---|---|---|---|---|
| Tmax (days) | $2.50 \pm 1.22^{a}$ | $4.67 \pm 0.82^{b}$ | $2.83 \pm 1.33^{a}$ | 0.010 |
| Cmax (ng/ml) | $3.67 \pm 1.57^{a}$ | $3.77 \pm 0.94^{a}$ | $4.32 \pm 1.15^{a}$ | 0.629 |
| $AUC_{0\text{-}15d}$ (ng.d/ml) | $16.2 \pm 3.42^{a}$ | $21.6 \pm 6.72^{ab}$ | $27.7 \pm 7.27^{b}$ | 0.017 |
| $T_{1/2}$el (days) | $2.43 \pm 0.10^{a}$ | $2.21 \pm 0.22^{a}$ | $2.15 \pm 0.29^{a}$ | 0.095 |
| Milk-to-plasma $ratio_{AUC}$ | $0.21 \pm 0.04^{a}$ | $0.16 \pm 0.03^{a}$ | $0.17 \pm 0.03^{a}$ | 0.059 |
| Dose excreted through milk (%) | $0.07 \pm 0.03^{a}$ | $0.05 \pm 0.01^{ab}$ | $0.04 \pm 0.01^{b}$ | 0.043 |

*Note:* Different letters indicate statistical differences at $p<0.05$.

Abbreviations: $AUC_{0\text{-}15d}$, area under the concentration *vs*. time curve from time zero to 15 days post-administration; Cmax, peak plasma concentration; MRT, mean residence time; $T_{½}$el, elimination half-life; Tmax, time to peak plasma concentration.

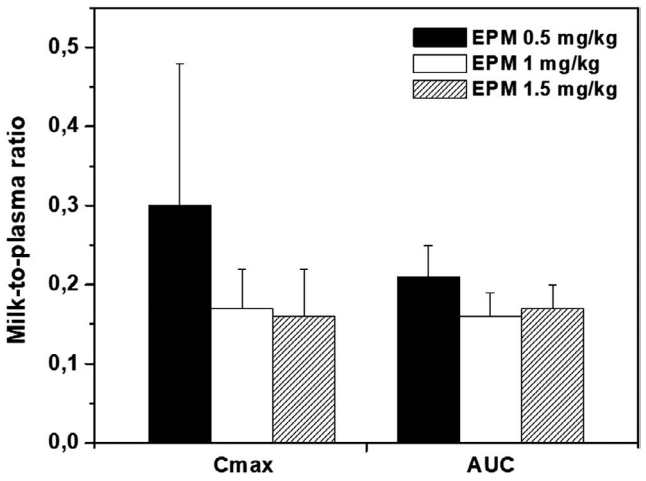


**FIGURE 3** Milk-to-plasma ratios (mean ±SD, *n*=6 per group) of peak concentrations (Cmax) and area under the concentration *vs*. time curves (AUC) calculated after topical (pour-on) administration of eprinomectin (EPM) to dairy cows at a dose of 0.5, 1 and 1.5 mg/kg

located in endemic areas, where tick (*Rhipicephalus (Boophilus) microplus)* infestation was found to reduce milk yield and liveweight gain during lactation (Jonsson et al., 1998). In Argentina, EPM is commercially registered as a 0.5% w/v pour-on formulation and may be an attractive therapeutical option for controlling ticks. The topical administration of EPM to dairy cows is especially advantageous because drug residues in milk after the recommended dose of 0.5 mg/kg are below the maximum level of residues of 20 ng/ml (Alvinerie et al., 1999).

Different treatment strategies against ticks were evaluated for EPM. After single and double applications of EPM at the dose recommended for the control of internal parasites (0.5 mg/kg), a high efficacy against ticks was observed in calves (Daves & George, 2002). In fact, those authors recommended doses two to three times higher to obtain higher tick control. This strategy was tested later by applying the topical EPM formulation to calves infected with ticks at 1 and 1.5 mg/kg (Aguirre et al., 2005; Lifschitz et al., 2016). In those trials, a high efficacy against ticks was obtained after EPM administration at both dose rates, without significant differences in the number of ticks between the administered doses, but with the 1.5 mg/kg having a higher effect on reproductive parameters (Lifschitz et al., 2016). The previous estimation of EPM disposition in milk using plasma concentrations in calves treated with EPM at 1 and 1.5 mg/kg concluded that the drug levels would be below 20 ng/ml (Lifschitz et al., 2016). However, to establish the effective and safe drug dosage regimens for EPM at higher dose rates in lactating dairy cows, plasma disposition kinetics and milk excretion pattern should be characterized to ensure that drug levels in milk are below the maximum residue limit. Our results corroborated milk EPM concentrations in dairy cows, with EPM milk Cmax ranging between 1.86 (0.5 mg/kg) and 5.86 ng/mL (1.5 mg/kg); this is a safe level, taking into account the maximum level allowed. This issue is very important due to the widespread use of long-acting formulation of MLs for controlling ticks in South America. The long-acting formulation provides sustained concentrations based on a slow release from the subcutaneous injection site (Lifschitz et al., 2007) and may prevent tick re-infestations (Nava et al., 2015). However, successive treatments with long-acting ivermectin (IVM) formulations increase its accumulation in cattle tissues (Nava et al., 2019), which may extend the withdrawal period indicated for the commercial product. Moreover, these formulations are not permitted for use in lactating dairy cows, which require the administration of products with a zero or very short milk withdrawal period. Thus, although the pharmacokinetics of EPM has been extensively studied in cattle at a dose of 0.5 mg/kg, the present study evaluated for the first time the comparative milk-to-plasma distribution pattern of EPM administered at 0.5, 1 and 1.5 mg/kg in dairy cows. The main results confirmed that the expected low concentrations of EPM excreted in milk were below the maximum residue levels, even at 2 and 3 times the approved dose.

The comparison of the plasma-milk disposition of EPM after administration of different dose rates of EPM to dairy cows showed interesting results. The mean plasma availability of EPM obtained in this study in dairy cows was 1.6- (136 *vs*. 213 ng/ml at 1 mg/kg) and 2.3- (165 *vs*. 382 ng/ml at 1.5 mg/kg) fold lower than that reported for beef cattle (Lifschitz et al., 2016). Such variability may reflect differences in animal physiology and body condition between beef cattle and lactating dairy cows. In fact, similar differences in the pharmacokinetic behaviour were

observed in lactating and non-lactating goats corroborating that the physiological status affects the disposition of lipophilic molecules (Dupuy et al., 2001).

Dose-normalized systemic availability did not show significant differences between groups treated with twofold and threefold higher doses than the recommended one. However, a simulation was done based on the observed data obtained after administration at 0.5 mg/kg, to simulate the behaviour of the other doses following a linear pharmacokinetics. The simulation resulted in a systemic availability 1.54-fold higher than that observed after administration at 1.5 mg/kg. Although a constant ratio of the milk-to-plasma concentrations was observed after the administration of the three dose rates, the percentage of dose excreted in milk was significantly lower after the administration of EPM at 1.5 mg/kg compared to that obtained after its administration at 0.5 mg/kg. The occurrence of a skin depot effect after the pour-on administration of MLs ivermectin and moxidectin to cattle was previously reported (Laffont et al., 2003; Sallovitz et al., 2003). The absolute bioavailability of ivermectin administered topically to cattle was 23% with 77% of the dose remaining on the skin (Laffont et al., 2003). After the topical administration of moxidectin, the AUC ratio between skin and abomasal mucosa was 4.55 for topical treatment *vs.* 1.02 for subcutaneous administration that also reflects the skin depot. In our work, a similar effect of skin depot may be occurring with increasing doses of EPM. The normalization of the AUC did not show significant differences between the administered doses due to the high variability and the small number of experimental animals necessary to detect these differences. However, the potential skin depot affected the dose linearity reducing the mean observed Cmax and AUC values after the administration of EPM at 1.5 mg/kg. On the other hand, there was not modification in the plasma Tmax, which could be indicating a great capacity of the skin to retain the drug without observing a significant extension in the absorption time.

From the efficacy point of view, the accumulation of EPM in the skin of treated animals may be an advantageous tool for controlling tick infestation. When EPM is topically administered, its uptake by ticks occurs as a combination of feeding habits and the contact with the drug depot on the skin surface. In fact, Lifschitz et al. (2016) observed that EPM accumulation in collected ticks from treated calves was directly related to the dose rate received. The high EPM concentrations measured in ticks during the first two days post-administration could be explained by the direct parasite-drug interaction in the skin (Lifschitz et al., 2016).

Besides the traditional topical preparation, injectable formulations of EPM were launched to the pharmaceutical market in different countries such as South Africa, Turkey and Brazil (Aksit et al., 2016; do Nascimento et al., 2020) to be administered subcutaneously at 0.2 mg/kg. The injectable EPM provides a greater systemic availability and peak concentration than the topical administration at 0.5 mg/kg but some of them have lost the advantage of the withdrawal period 0 in milk after their administration in lactating dairy cows. Therefore, the administration route, pharmaceutical formulation and dose of EPM should be chosen according to the type of parasites to be treated and the production system where this drug is going to be used.

## 6 | CONCLUSION

The topical administration of EPM to lactating dairy cows at higher doses than those recommended for the control of gastrointestinal nematodes showed a milk excretion pattern that allows avoidance of the withdrawal period in milk. As this therapeutic scheme was successfully evaluated in tick infestation, the administration of the topical formulation of EPM at 1 or 1.5 mg/kg may be a valuable tool to be used in strategic control programs in dairy production systems.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTION

All authors have read and approved the final manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in reference number JVPT-2021–3597.

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