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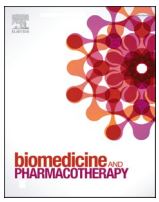

Ivermectin systemic availability in adult volunteers treated with different oral pharmaceutical formulations

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ABSTRACT

Ivermectin (IVM) is currently approved as an antiparasitic agent for human use in the treatment of onchocerciasis, lymphatic filariasis, strongyloidiasis, scabies, and pediculosis. Recent findings indicate that IVM may reach other pharmacological targets, which accounts for its proven anti-inflammatory/immunomodulatory, cytostatic, and antiviral effects. However, little is known about the assessment of alternative drug formulations for human use.

Objective: To compare the systemic availability and disposition kinetics of IVM orally administered as different pharmaceutical formulations (tablet, solution, or capsule) to healthy adults.

Experimental design/main findings: Volunteers were randomly assigned to 1 of 3 experimental groups and orally treated with IVM as either, a tablet, solution, or capsules at 0.4 mg/kg in a three-phase crossover design. Blood samples were taken as dried blood spots (DBS) between 2 and 48 h post-treatment and IVM was analyzed by HPLC with fluorescence detection. IVM Cmax value was higher ($P < 0.05$) after the administration of the oral solution compared to treatments with both solid preparations. The oral solution resulted in a significantly higher IVM systemic exposure (AUC: 1653 ng h/mL) compared to the tablet (1056 ng h/mL) and capsule (996 ng h/mL) formulations. The simulation of a 5-day repeated administration for each formulation did not show a significant systemic accumulation.

Conclusion: Beneficial effects against systemically located parasitic infections as well as in any other potential therapeutic field of IVM application would be expected from its use in the form of oral solution. This pharmacokinetic-based therapeutic advantage without the risk of excessive accumulation needs to be corroborated in clinical trials specifically designed for each purpose.

1. Introduction

Ivermectin (IVM) has been used as an anthelmintic agent both in veterinary and human medicine for over 35 years [1,2]. After its introduction into the pharmaceutical market, it became the most used drug in veterinary medicine due to its broad spectrum of activity, high potency, efficacy, and safety [3]. In humans, it was first used to treat *Onchocerca volvulus* [2], but nowadays it is widely distributed through the Mectizan Donation Program for the treatment of onchocerciasis and lymphatic filariasis [4] and is one of the World Health Organization's Essential Medicines, used for the treatment of scabies and lice [5]. In addition, IVM is being increasingly used in combination with benzimidazole drugs to control soil-transmitted helminthiasis considered a neglected disease such as those produced by *Strongyloides stercoralis* and *Trichuris trichiura* [6–9].

IVM is prescribed in weight-based dosing regimens for any person ≥ 2 years old at 50–400 μg/kg. Doses up to 400 μg/kg are used against *Wuchereria bancrofti* infections [10] and, doses > 400 μg/kg are under evaluation to control soil-transmitted helminths and malaria [8,9,11]. IVM has a favorable safety profile with rare and mostly mild adverse events, leading to a wide therapeutic index in humans [10,12]. The rare adverse events are headache, nausea, and dizziness. Mydriasis was reported in documented human overdosing cases [8,12].

The pharmacological activity of IVM is not restricted to an ecto-endo parasiticide effect. Considering its versatile pharmacological activity including anti-inflammatory [13], immunomodulatory [14], antimitotic

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[15–17], antimalarial [18–21], and antiviral, mostly towards RNA viruses [22,23], and based on its pleiotropic multitarget pharmacological activity, IVM repurposing is now receiving full consideration for the treatment of a wide variety of diseases in different therapeutic fields. Following the emergence of the COVID-19 pandemic, the use of IVM for the prevention/treatment of SARS-CoV-2 infections has notably increased in many regions of the world, supported by either in vitro [24] or in vivo [25] studies, suggesting that it could be used as a possible therapeutic option in infected humans. Additionally, an important number of studies (32 completed studies available at https://clinicaltrials.gov/) have evaluated the potential IVM clinical usefulness in COVID-19-infected patients. Overall, both in vitro and in vivo evidence postulate that the activity of IVM would be mainly based on the inhibition of virus replication, with a significant reduction in SARSCoV-2 viral load in respiratory secretions of infected patients. A correlation between IVM systemic exposure and viral load reduction has been shown [25]. However, the efficacy of IVM for the prevention of SARS-CoV-2 infection and COVID-19 treatment is still under debate.

Such treatments include primarily the use of a tablet formulation. However, other oral IVM pharmaceutical formulations are currently available for human parasite control in some countries. Differences in the manufacturing procedures (micronized, particle size/surface/crystal structure of the active substance, type of excipients/vehicle, etc.) applied to elaborate the final formulation and/or the quality of active ingredient/excipients/vehicles may drastically affect the amount of active drug available to be absorbed in the gastrointestinal tract. It has been demonstrated a close relationship between systemic drug exposure and either antiparasitic [26–28] or antiviral [25,29] activities. These results highlight the potential impact of drug formulation on drug activity, since the drug formulation may affect the patterns of drug dissolution, absorption, and efficacy [30]. There is a need to build scientific evidence on the IVM concentration profiles achieved in systemic circulation after its administration as different pharmaceutical formulations. Pharmacokinetic studies focused on the measurement of drug concentration profiles achieved in the bloodstream are useful in estimating drug exposure in other specific sites/tissues of pathogen location.

Despite the great potential that IVM offers as a pleiotropic therapeutic agent, little is known about the assessment of alternative drug formulation for human use. The estimation of the systemic availability may be useful to compare the extent of absorption and systemic exposure of different formulations of the same active ingredient administered at the same dose rate. The goal of the current study was to compare the blood pharmacokinetic profiles (systemic exposure) of three marketed IVM formulations (tablets, solution, and capsules) orally administered to healthy adult volunteers.

2. Materials and methods

2.1. Ethical aspects

The study protocol and informed consent form (ICF) were approved by the regulatory authorities of the Province of Buenos Aires, Argentina, Comité de Ética en Investigación, Instituto de Investigaciones Clínicas, CEI-IIC, Mar del Plata, Argentina (CIF IVM1.03.7june2021, Protocol IVM1.02.31may2021). The study was conducted following the Declaration of Helsinki and the International Conference on Harmonization Guidelines in Good Clinical Practice.

2.2. Eligibility criteria

The study included twelve [12] healthy adults 29–62 years old. Exclusion criteria included intake of IVM within the 30 days previous; evident renal pathology, malabsorption syndromes, or other gastrointestinal disorders; the presence of acute or chronic clinical conditions; pregnancy or breastfeeding; treatment with warfarin or any drug compound with potential chromatographic interference with IVM.

2.3. Study design and sampling

This trial was conducted following good clinical and laboratory practices. Twelve healthy adult volunteers (six females and six males, aged 29–62 years) participated in a crossover design with three different experimental phases. IVM was orally administered at 0.4 mg/kg body weight (bw), 30 min after a standard breakfast (estimated fat content 40 g). The administered dosage for the different formulations under evaluation did not differ by more than 5 % from the established 0.4 mg/kg bw. In phase I, participants were randomly assigned to 1 of 3 experimental groups: **Tablet Group**: volunteers received a single oral dose of a commercially available IVM tablet (6 and 9 mg Tablets were used), **Solution Group**: volunteers were orally treated with a single dose of a commercially available 0.6 % IVM solution and, **Capsule Group**: individuals received oral treatment with a commercially available IVM capsule (6 and 9 mg capsules were used).

The tablets (Elea®) were formulated with lactose monohydrate, cellactose 80, sodium starch glycolate, magnesium stearate, and talcum powder; the capsules Berlari Pharmacy) were formulated with lactose monohydrate and the copulas were of standard gelatin. The IVM solution vehicle (Cassara®) was propylene glycol, essence of mint, essence of vanilla, saccharin sodium, and sorbitol 70 %.

Participants were crossed over between the other 2 groups, with a 14-days washout period between phases. The dried blood spot (DBS) method was used to collect blood samples**.** Capillary blood was collected from each participant previously (sampling time 0) and at 2, 4, 6, 8, 12, 24, and 48 h post-treatment. Sterile finger prickers (Accu-Chek® Softclix) were used to puncture the tip of a finger obtaining a blood drop, which was dropped onto special cards (Western blotting filter paper, Thermo Scientific, USA). This was performed in two replicates for each participant at each sampling time point. The DBS cards were allowed to dry for at least 2 h and then stored at room temperature in sealed plastic bags until analysis by High-Performance Liquid Chromatography (HPLC), which was performed within the following 48 h.

2.4. Analytical phase

Samples extraction: the dried blood drops were punched from each DBS card and weighed, then transferred to 5 mL glass tubes. The samples were spiked with moxidectin as the internal standard (10 μL, 5 ng/mL solution). The IVM extraction was performed by adding 1 mL of an acetonitrile/water solution (4/1, cold) as a solvent. Then, the samples were agitated at room temperature for 15 min and sonicated in an ultrasonic bath for 90 min. Finally, the supernatant was evaporated to dryness for further analysis by HPLC.

Measurement of IVM: IVM concentrations were determined by HPLC (Shimadzu Corporation, Kyoto, Japan) with fluorescence detection following the chromatography technique previously described by Lifschitz et al., [31]. After the extraction procedure, IVM was converted into a fluorescent molecule using n-methylimidazole and trifluoroacetic anhydride (Sigma Chemical, St Louis, MO, USA). An aliquot (100 mL) of this solution was injected directly into the HPLC system and analyzed using a reverse phase C18 column (Kromasil, Eka Chemicals, Bohus, Sweden, 5 μm, 4.6 mm × 250 mm) and an acetic acid 0.2 % in water/methanol/acetonitrile (1.6/60/38.4) mobile phase at a flow rate of 1.5 mL/min at 30 °C. The fluorescent detector was set at 365 nm (excitation) and 475 nm (emission wavelength).

Validation procedure: full validation of the analytical methods for the extraction and quantification of IVM was performed before the analysis of the experimental samples, following internationally recognized criteria including selectivity, linearity, precision, accuracy, limit of detection, limit of quantification and stability [32]. The chromatographic identification of IVM was undertaken by comparison with retention times of pure (99 %) reference standard. The calibration for

the IVM curveswase in the 2–50 and 40–300 ng/mL ranges using 10 different concentrations (n = 6) (2, 4, 10, 20, 40, 50, 80, 100, 200, and 300 ng/mL). Calibration standard curves and quality controls (n = 6: 4, 20, 80, and 300 ng/mL) were prepared using drug-free blood voluntarily contributed by some of the volunteers (before treatment) supplemented with IVM prepared in methanol to achieve the final concentration above mentioned. Seventy μL of each were dropped onto the cards. The dry DBS cards were stored at room temperature in sealed plastic bags until the IVM extraction and analysis by HPLC.

Pharmacokinetic analysis: pharmacokinetic analysis of the experimental data was performed by non-compartmental analysis. The following pharmacokinetic parameters were obtained using the PK Solution software (Summit Research Services, Ashland, USA): peak IVM blood concentration (Cmax), time to reach Cmax (Tmax), elimination half-life ($T_{1/2el}$), area under the curve concentration vs time from time zero to either the limit of quantification ($AUC_{0–LOQ}$) or extrapolated to infinity ($AUC_{0–\infty}$) and mean residence time (MRT).

Statistical analysis of the data: the pharmacokinetic parameters and concentration data are reported as the arithmetic mean ± SD. Parametric paired tests (analysis of variance [ANOVA] plus Tukey) were used for the statistical comparison of the different pharmacokinetic parameters among the experimental groups. The Cmax and $AUC_{0–LOQ}$ values observed for male and female individuals in each experimental group were compared by Student's t-test.

The measured blood profiles obtained after a single IVM administration were used to simulate the concentrations achieved after the repeated administration of daily (× 5) oral doses (0.4 mg/kg) using the Modfit 6.9 software [33]. Pharmacokinetic parameters were calculated from a non-compartmental approach. The simulation was addressed to assess the potential drug accumulation due to an IVM multiple-dose regimen schedule. Assuming that a single dose profile of a drug is available for each formulation (observed data), then the principle of superposition was used. The assumptions that the kinetics are linear and unchanging over a repeat dose regimen in addition to the premise that all doses are independent of each other were made. Drug accumulation was calculated as AUC or Cmax ratios betweenthe last and first doses. Besides, to obtain a PK/PD indicator, the software estimated the AUC above MIC. The MIC of 80 ng/mL and 40 ng/mL were selected as representative of therapeutic targets which need high and medium drug exposure.

3. Results

The analytical methodology was correctly validated before the measurement of IVM concentrations in DBS samples. The blank samples were free of chromatography interferences at the retention time of the analytes under study. The coefficient of determination (r^2) of the calibration curve was ≥ 0.997. The mean absolute recovery percentage for IVM was 77 %. The IVM theoretical limit of quantitation (LOQ) was 4 ng/mL. The precision of the method showed a coefficient of variation of 7.4 %.

IVM was detected in DBS samples of healthy adults treated with a single postprandial dose of the commercially available tablet, solution, or capsule (0.4 mg/kg) between 2 and 48 h post-administration. The mean concentrations (± SD) over the sampling time are summarized in Table 1. The IVM concentrations achieved after treatment with the solution formulation were higher (P < 0.05) at most of the sampling times assessed compared to those observed after its administration as tablets and capsules (Fig. 1). The main pharmacokinetic parameters (± SD) obtained after administration of the different IVM formulations are summarized in Table 2. Except for one participant with a Tmax at 8 h p.t. (Tablet group), the peak concentrations (Cmax) were observed between 2 and 6 h after administration of all IVM formulations. The Cmax value was significantly higher in the group treated with the solution (120.4 ± 53.5 ng/mL) compared to that observed after administration of either tablet (71.8 ± 18 ng/mL, P = 0.0056) or capsules (66.0 ± 27.1 ng/mL, P = 0.0002).

Table 1
Mean (± SD) ivermectin (IVM) blood concentrations obtained after its single oral administration (0.4 mg/kg) as either Tablet, Solution, or Capsule formulations to healthy adult volunteers (n = 12).

Time post-treatment (h)	IVM concentration (ng/mL)					
	Tablet		Solution		Capsule	
	Mean	SD	Mean	SD	Mean	SD
0	0.00	0.00	0.00	0.00	0.00	0.00
2	49.3[a]	17.0	105.0[b]	56.2	42.1[a]	23.2
4	66.4[a]	18.6	109.8[b]	55.6	62.3[a]	29.5
6	54.4[ab]	22.0	77.4[ac]	41.6	50.9[b]	18.4
8	41.6[a]	16.2	59.4[b]	20.1	39.1[a]	14.2
12	26.7[a]	12.3	39.9[b]	12.3	27.3[a]	9.90
24	15.3[a]	6.20	23.3[b]	6.20	15.0[a]	7.50
48	8.50[a]	2.80	12.7[b]	3.00	9.10[a]	3.90

Blood samples obtained by the Dried Blood Spot (DBS) technique. Different letters mean a statistically significant difference at P < 0.05.

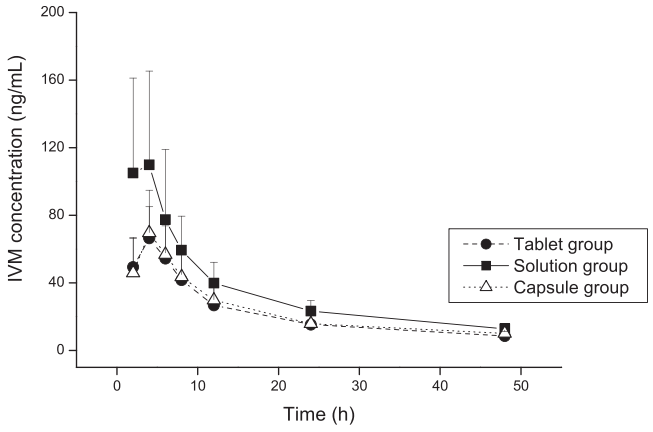

Fig. 1. Comparative mean (± SD) ivermectin (IVM) blood concentration-time profiles obtained after its oral administration at 0.4 mg/kg as either Tablet, Oral Solution or Capsule formulations to healthy adult volunteers (n = 12).

Table 2
Mean (± SD) ivermectin pharmacokinetic parameters obtained after its single oral administration (0.4 mg/kg), formulated as either Tablets, Solution or Capsules, to healthy adult volunteers.

Pharmacokinetic parameters	Tablet		Solution		Capsule	
	Mean	SD	Mean	SD	Mean	SD
Cmax (ng/mL)	71.8[a]	18.0	120.4[b]	53.5	66.0[a]	27.1
Tmax (h)	4.50[a]	1.50	3.30[a]	1.30	4.30[a]	0.78
AUC_{0-LOQ} (ng h/mL)	1056[a]	344.7	1653[b]	498.6	996.5[a]	432.6
$AUC_{0-\infty}$ (ng h/mL)	1261[a]	401.5	1958[b]	516	1246[a]	544.1
MRT (h)	24.4[a]	3.10	24.6[a]	6.50	25.3[a]	4.60
T½el (h)	16.5[a]	1.80	17.4[a]	4.90	17.0[a]	3.80

Cmax: maximum blood IVM concentration; Tmax: time to reach Cmax; $AUC_{0–LOQ}$ area under the curve concentration vs time from time zero to the limit of quantification; MRT: mean blood residence time; $T_{1/2el}$: elimination half-life. Different letters indicate statistically significant differences (P < 0.05) among experimental groups.

The sampling schedule chosen provided a reliable estimation of the extent of exposure since AUC_{0-LOQ} covers ≥ 80 % of $AUC_{0-\infty}$ in all experimental groups. Fig. 2 compares the kinetic variables Cmax and $AUC_{0–LOQ}$ for IVM after administration of tablets, solution, and capsules. The higher concentrations reached in the solution group were reflected in greater systemic availability, expressed as AUC_{0-LOQ} (1653.3 ± 498.6 ng h/mL) compared to that obtained after the tablet (1056.1 ± 344.7 ng h/mL, P = 0.0008) and capsules (996.5 ± 432.6 ng h/mL,

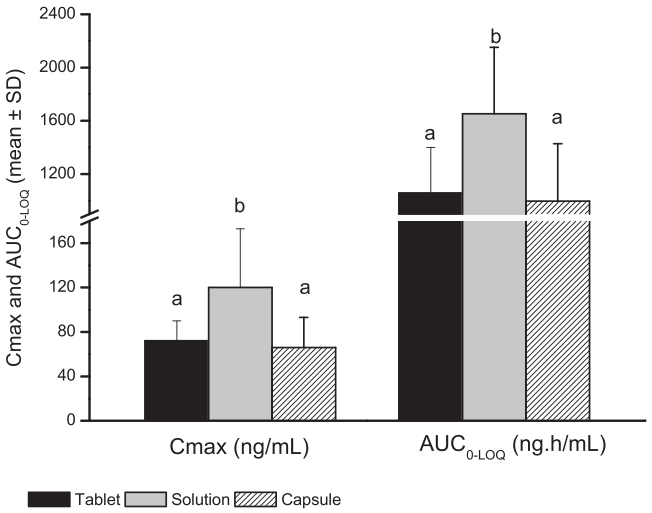

Fig. 2. Comparative mean (± SD) ivermectin peak blood concentration (Cmax) and area under the blood concentration-time curve (AUC) values obtained after its oral administration (0.4 mg/kg) as either Tablet, Solution or Capsule formulations to healthy adult volunteers (n = 12). Different letters indicate statistically significant differences at $P < 0.05$.

$P = 0.0002$) administration. Those values were between 56 % and 66 % higher in the volunteers receiving the solution treatment compared to those treated with tablets or capsules, respectively. The $T_{½el}$ and MRT parameters resulted similar among the three formulations under evaluation (Table 2). The pharmacokinetic parameters Cmax, Tmax, $AUC_{0–LOQ}$, $AUC_{0–\infty}$, MRT, and $T_{1/2el}$ were not statistically different between tablets and capsules ($P > 0.05$).

Both in women and men, the administration of the solution formulation correlated with a significant increase in systemic exposure, compared to solid formulations (tablet and capsule). The pharmacokinetic parameters obtained for tablets and capsules were similar ($P > 0.05$) between genders. However, after treatment with the solution, the peak concentration achieved in women (153.7 ± 54.6 ng/mL) was higher ($P < 0.05$) than that observed in men (87.1 ± 25.5 ng/mL) (Fig. 3). Although the mean IVM systemic availability value tended to be higher in women (1849.3 ± 604.6 ng.h/mL) compared to men (1457.3 ± 298.8 ng.h/mL), the differences did not reach statistical significance ($P > 0.05$).

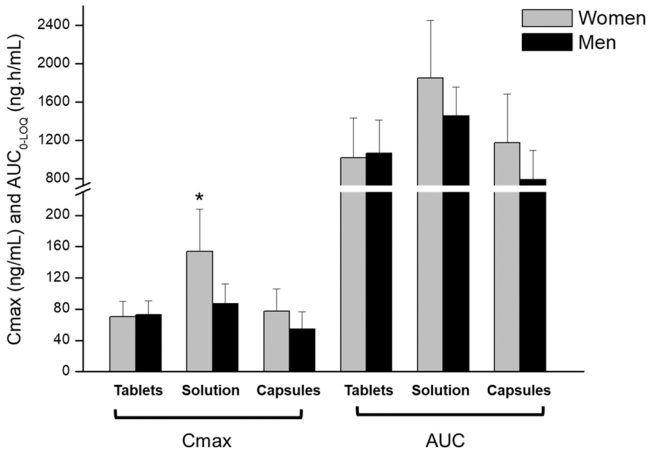

Fig. 3. Comparative mean (± SD) ivermectin peak blood concentration (Cmax) and area under the concentration-time curve (AUC) values observed in women and men, after its oral administration (0.4 mg/kg) as either Tablet, Solution or Capsule formulations to healthy adult volunteers (n = 6 for each gender). *Differences are statistically significant at $P < 0.05$.

Fig. 4 shows a model predicting blood IVM concentration profiles achieved following a multiple-dosing (× 5) regimen for each formulation. The simulated drug accumulation calculated as the ratios of the $AUC_{0–24}$ on day 5 and the $AUC_{0–24}$ on day 1 was 1.62, 1.60, and 1.69 for the tablet, solution and capsule formulations, respectively. The ratios of the Cmax on day 5 and Cmax on day 1 were 1.38, 1.35, and 1.42, respectively. These results suggest no relevant accumulation of IVM after five consecutive days of dosing. Taking the theoretical IVM concentrations of 80 ng/mL and 40 ng/mL as the minimum inhibitory concentrations (MIC) for some given targets, the AUC/MIC as a PK/PD parameter was calculated for the multiple-dosing regimen. The mean (± SD) of AUC/MIC_{80} over simulated five treatment days was significantly greater ($P < 0.05$) after the administration of the solution (248 ± 103) compared to tablets (8.3 ± 8.2) and capsules (3.8 ± 4.3). Similarly, the differences were maintained if the analysis was carried out on a target that needed less exposure to IVM. The mean (± SD) of AUC/MIC_{40} was also significantly greater ($P < 0.05$) after the solution treatment (785 ± 255) compared to tablets (253 ± 101) and capsules (231 ± 107).

4. Discussion

Advances in science and technology have stimulated a permanent search for therapeutic tools to combat a variety of human and animal diseases. Given the complexity of the discovery and development process of new drugs which implies many years and high costs, an alternative approach is the “repurposing” of approved or investigational drugs, identifying new uses that are outside the scope of the original medical indication [34].

IVM, a well-known ecto-endoparasiticide compound, has now been repurposed to control dengue [35,36] and malaria infection [37,38]. Thus, the perspective of IVM use has been expanded beyond its broad-antiparasitic spectrum in veterinary and human medicine to a wide range of targets and activities, including anti-plasmodial [19], antiviral [23,24], anti-mycobacterial, cytostatic [16,39] and antiinflammatory/immunomodulatory [40]. IVM has also been postulated as a potential candidate among currently used drugs to promote the repair of myelin damage [41]. The variety of potential alternative IVM targets implies the need for a deep understanding of its pharmacokinetic behavior. IVM repurposing requires a clear interpretation of its capacity to reach different tissues in the human body.

The pharmacokinetic properties of IVM have been extensively studied in different animal species [42–45] and data on the kinetic behavior in humans are available [12, 46–48]. However, most studies in humans were performed using the IVM tablet formulation varying the experimental conditions by using different doses or regimens of

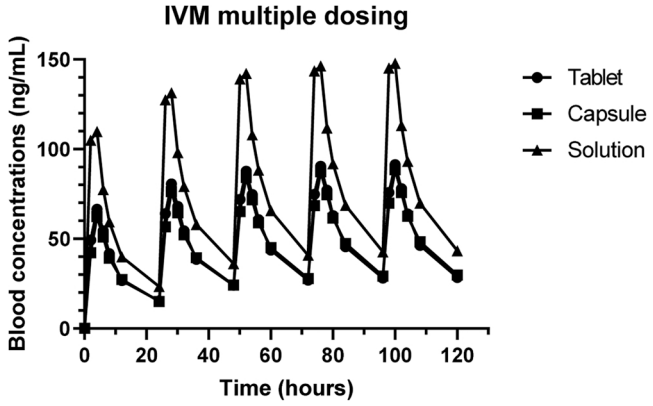

Fig. 4. Simulated ivermectin (IVM) blood concentration versus time profiles following administration of repeated daily (× 5) oral doses (0.4 mg/kg) as either Tablet, Solution or Capsule formulations to healthy volunteers.

administration. While a previous report compares different IVM formulations [46], this earlier work was performed with markedly different experimental designs including fixed dose administration (12 mg) of widely different pharmaceutical preparations in fasted individuals. Additionally, the comparative pharmacokinetic data reported in the current study are based on the measurement of blood concentrations collected by the DBS collection technique.

IVM formulation may drastically affect its absorption and the resulting concentrations that reach the bloodstream and the tissues [30,31,49]. Considering the increase in potential therapeutic targets for IVM described in the latest years, beyond those widely known (gastrointestinal nematodes or ectoparasites), the characterization and development of new formulations aiming to improve its systemic availability are considered of relevant value. In 1987, the first formulation of IVM in tablet form (Mectizan®) was approved; however, other formulations for both oral (solutions and capsules) and topical use were later commercially developed. The work reported here provides updated information on the comparative kinetic behavior and systemic exposure of IVM after oral treatment to adult volunteers with three different marketed IVM formulations (tablets, solution, and capsules).

A key factor that determines clinical favorable responses (efficacy) against systemic targets is the achievement of adequate/sustained drug concentrations (exposure) at the target tissues. It has been established in different animal species that the higher the drug concentrations achieved in the tissue of parasite location, the higher the amount of drug accumulated within the target parasite [50–52]. There are different pharmacokinetic-based strategies to increase the drug systemic availability, and consequently improve the therapeutic response. The administration with food [53], the use of higher IVM doses [10,54], and different regimens of administration [12,55] have been evaluated. Based on those previous findings, we wanted to evaluate here the impact of the type of drug formulations on IVM systemic exposure in healthy volunteers. A drug orally administered has to be released from its formulation, dissolved in gastrointestinal fluids, and absorbed, before entering into the bloodstream, distributed to tissues, and attaining an effective concentration at its site of action for a sufficient time [56].

The results reported here suggest that dissolution is an important factor determining the systemic availability of IVM in humans. A different situation has been reported in horses, in which a similar extent of IVM absorption and plasma disposition was reported after its oral administration as a paste or as a solution, despite the different composition of their excipients [57]. Higher IVM blood profiles were observed after the solution administration compared to tablet or capsule administration. The increase in drug availability did not correlate with clinical adverse experiences during the study, which is related to the safety and tolerability reported for IVM even at doses as high as 2 mg/kg [12].

Even when the bioequivalence among formulations was not evaluated, the Cmax and AUC ratios between Solution and Tablet (reference formulation) were 1.56 (Cmax) and 1.67 ($AUC_{(0\text{-}LOQ)}$), indicating a possible lack of bioequivalence between these formulations. However, this assessment was out of the scope of the study reported here and should be accurately evaluated in specifically-designed studies. These are relevant results since there is a close relationship between IVM availability in the bloodstream and the drug concentrations achieved in different tissues such as the skin, gastrointestinal mucosa, nasopharyngeal and lung tissues [31,58].

Some sex-related differences in the kinetic behavior of some macrocyclic lactone compounds have been observed in cattle [59], dogs [60], and rats [61]. In agreement with that, we reported here a clear tendency to achieve higher peak concentrations and systemic exposure in women compared to men, even though a statistically significant difference was only observed for the Cmax values in volunteers receiving the oral solution treatment (Fig. 3). IVM is a well-established P-glycoprotein (P-gp) substrate [62], and among many other possibilities to be elucidated, the observed sex-related differences may be due to differential activity of this efflux pump protein acting as drug transporter in different tissues, as it has been discussed in the available literature [61].

Similar to previous studies [12,63,64], most of the IVM pharmacokinetic parameters showed a large inter-individual variability. The pharmacokinetic differences observed among formulations were in agreement with data previously reported by Edwards et al. [46]. The IVM $AUC_{0\text{-}LOQ}$ coefficient of variation (CV) was higher (43.4 %) after treatment with capsules, compared to both solution (CV = 30.2%) and tablets (CV = 32.6 %). However, after the treatment with the liquid solution preparation a large high variability was observed in the peak concentration value (CV = 44.4 %). This is not surprising since numerous factors can influence absorption from the gastrointestinal tract, making it rather unpredictable. Among many others, these factors include tablet/capsule size, the dissolution rate of solid formulations, the presence of water-soluble excipients in the formulation, the presence of food in the stomach, gastrointestinal motility, and the activity of some intestinal efflux pumps. All these factors may primarily impact the pattern of IVM gastrointestinal absorption. It is important to highlight that the sampling time used in the current experiment was not the most appropriate for evaluating drug absorption. IVM absorption was fast (Tmax between 3.3 and 4.5 h) regardless of the formulation and the first sampling point was taken 2 h after administration. The current work reports for the first time the systemic availability and overall pharmacokinetic behavior of IVM in adult volunteers orally treated with different pharmaceutical formulations at a dose rate of 0.4 mg/kg. Considering the overall differences in the used experimental design (dose rate, food intake, type of formulations, sampling points, etc.), as well as the inter-individual variability, the values describing key pharmacokinetic parameters obtained for IVM in the current work, are in agreement with those reported in previous studies [8,46,64].

Overall, the work reported here demonstrates that the IVM pharmacokinetic behavior in humans can be markedly modified by changes in drug formulation. The treatment with an oral solution in healthy volunteers resulted in improved absorption of IVM compared to that observed for the solid formulations, without risk of excessive accumulation. Beneficial effects against systemic parasitic infections as well as in any other potential therapeutic field of IVM application would be expected from its use in the form of oral solution. The estimation of a PK/PD-based parameter, such as the AUC/MIC relationship, shows a potential therapeutic advantage for IVM given as a solution. However, considering the observed large inter-individual variability on IVM systemic concentrations in humans, the expected clinical advantage from the use of the solution formulation needs to be corroborated. In this sense, the increase in the dosing level, regardless of the formulation used, may also have a great impact on the increase in systemic concentrations and efficacy against systemically located infections. The toxicological profile of IVM allows dose adjustments without significant increases in associated side effects [9,12], which is also supported by the low risk of excessive drug accumulation shown here when a multiple-dosing simulation approach was performed.

Overall, the described potential pharmacokinetic-based therapeutic advantage without risk of excessive accumulation needs to be corroborated in clinical trials specifically designed for each purpose. This information may be of particular relevance considering the growing interest in the repurposing of IVM as a tool in a variety of different therapeutic fields.

CRediT authorship contribution statement

Laura Ceballos: Conception and design of the study, Writing – original draft, Writing – review & editing, Analytical development, Validation, HPLC analysis. **Luis Alvarez:** Conception and design of the study, Analytical development, Validation, HPLC analysis, Writing – review & editing. **Adrian Lifschitz:** Conception and design of the study, simulation analysis, Writing – review & editing. **Carlos Lanusse:** Conception and design of the study, Integration/analysis/discussion of the data, Supervision, Writing – review & editing.

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Conflict of interest statement

Please declare any financial or personal interests that might be potentially viewed to influence the work presented. Interests could include consultancies, honoraria, patent ownership or other. If there are none state 'there are none'.

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