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Original Article

Synthesis and Clinical Examination of Novel Formulations of Ivermectin, Albendazole and Niclosamide for the Treatment of Equine Gastrointestinal Helminthoses

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Abstract

Background: This study aimed to develop new complex preparations of ivermectin, niclosamide and albendazole based on solid-phase mechanochemical technology, and to evaluate their efficacy against equine nematodosis and cestodosis.

Methods: Novel formulation of antiparasitic paste were prepared using joint mechanochemical treatment of ivermectin (0.2 mg/kg bodyweight; BW), niclosamide (10 mg/kg BW) and albendazole (3, 5, 10 mg/kg BW) substances with polyvinylpyrrolidone and arabinogalactan. For the evaluation of activity of different doses of formulations against gastrointestinal tract helminths a total of 151 adult horses of the Novoaltai breed weighing 450–500 kg naturally infected with strongyles (>150 egg per gram of faeces, EPG), *Parascaris* spp. (>20 EPG) and *Anoplocephala* spp. (>10 EPG) were selected. Antiparasitic pastes were orally fed to the horses and faecal egg count reduction counts were compared prior to and 14 days after the treatment.

Results: Pastes with mechanically modified ivermectin showed 91.4–100% efficacy against strongyles and *Parascaris*. Pastes with modified albendazole and niclosamide were also effective against *Anoplocephala* in all tested dosages i.e. 78.6–100%. In particular, treatment with two formulations containing i) 0.2 mg ivermectin, 10 mg albendazole, 10 mg niclosamide, and ii) 0.2 mg ivermectin, 3 mg albendazole showed 100% efficacy against strongyles, *Parascaris* and *Anoplocephala*.

Conclusion: Solid-phase mechanochemical technology could be applied in equine anthelminthics production. It is suggested that future studies focus on plasma concentration-time profile of these highly effective pastes.

Introduction

Horses become infected with different types of helminths such as *Parascaris* species, strongyles (roundworms) and *Anoplocephala* species (tapeworms) which can cause digestive and respiratory diseases and contribute to performance conditions (1). Helminthoses are commonly controlled by antiparasitic compounds however, there are increasing reports regarding development of resistance to drugs that are used to combat them (2). Hence, it is necessary to develop new and more effective antiparasitic compounds to control them.

In different regions of the Altai Mountains in Russia infection of horses with helminths is common e.g. prevalence of strongyles is reported to be 79.4–100.0%, *Parascaris* 7.2–22.1%, and *Anoplocephala* 4.0–23.8% (3-5). Such levels of infection imply regular antiparasitic treatments using drugs with a wide spectrum of activity.

Currently various formulations of parasiticides based on the active ingredients (AI) of macrolides and benzimidazoles are widely used (6-8). Previously it was shown that, solid-phase mechanochemical modification of known medicinal substances increases the solubility of antiparasitic compounds thus leading to more effective complex preparations for the treatment of helminthic infections (9, 10).

The aim of this study was to i) develop innovative multicomponent anthelmintic formulations based on albendazole, ivermectin and niclosamide with improved solubility in the form of oral pastes, and ii) to study their parasiticidal activity against gastrointestinal nematodes and cestodes of horses with the produced pastes.

Materials and Methods

Ethical standards

This study was approved by the Russian Foundation for Basic Research and the Republic of Altai (project No. 20-44-040004) and the State order of the Federal State Scientific Institution (FANCA No 0534-2021-0005). All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Chemical and technological characteristics

i) Albendazole (ALB): methyl [5-(propylthio)-1H-benzimidazol-2-yl]-carbamate, solubility in water = 1.0 mg/L, Changzhou Jialing Medicine Industry Co. Ltd., Changzhou, China.

ii) Ivermectin (IVM): solubility in water = 4.0 mg/L, Shandong Qilu King-Phar Pharmaceutical Co. Ltd., Changzhou, China.

iii) Niclosamide (NS): 5-chloro-N- (2-chloro-4-nitrophenyl) -2-hydroxybenzamide, solubility in water = 5.0 mg/L, Ghangzhou Yabang-Qh Pharmachem Co. Ltd., Changzhou, China.

To improve the solubility parameters of above AI we used four substances i.e. i) polyvinylpyrrolidone (PVP) -1 ethenylpyrrolidin-2-one brand K-30 (30 kDa), Boai NKY Pharmaceuticals Ltd., Changzhou, China, ii) arabinogalactan (AG; Lavitol-arabinogalactan®), JSC Ametis, Moscow, Russia, iii) polyethylene glycol (PEG-400®), Norchem group of companies, Moscow, Russia, iv) propylene glycol, LLC Nefte-Chemical Company NERS +, Moscow, Russia. These polymers are safe with no toxicity concerns on the basis of the available data (11-13).

Prototype pastes production was carried out by a 2-stage method. Initially, the mechanochemical treatment of the substances ALB, IVM and NS individually or in combination (e.g. mixture of ALB and IVM with selected polymers) was carried out in a drum installed on the rolls of the MVF-4 mill (Techno-Centre, Rybinsk, Russia) at different concentration ratios of components (14). The solid

dispersions (SD) obtained in this method were free-flowing beige powders with increased water solubility (15). Then samples of antiparasitic compositions were prepared in the form of pastes from SD substances of anthelmintics and polymers with the addition of appropriate solvents (propylene glycol, PEG-400), surfactants (Tween 60, Tween 80) and thickeners (sodium carboxymethylcellulose: NaCMC) using a rotary high-speed mixer. The resulting parasiticidal products (Table 1) were thick but flowing pastes.

Table 1: Formulation and active ingredient concentration of produced oral pastes.

Product name	*Solid dispersions formulation*	*Active ingredient (mg/ml)*		
		IVM	ALB	NS
PPIA-1	ALB:PVP:AG=1:1:0.75 + IVM:PVP:AG=1:5:3.75	10	500	–
PPIAN	ALB:PVP:AG=1:1:0.75 + IVM:PVP:AG=1:5:3.75 + NS:PVP:AG=1:0.8:0.8	10	500	500
PPIA-2-1	ALB:IVM:AG=1:1:10 ; PS and water were added to the required consistency*	10	50	–
PPIA-2-3	ALB:IVM:AG=1:1:10 ; PS and water were added to the required consistency*	6.75	100	–
PPIA-2-5	ALB:IVM:AG=1:1:10 ; PS and water were added to the required consistency*	5	125	–

ALB=albendazole, IVM=ivermectin, NS=niclosamide, PVP=polyvinylpyrrolidone, AG=arabinogalactan, PS=potato starch.
*- PS was added 10% by weight of the SD of the drug, water was added 0.63 mL per 1 g of the final dry composition

Control sample pastes were initial substances i.e. 10 mg IVM, 500 mg ALB for PPIA-1 and PPIA-2, and 10 mg IVM, 500 mg ALB, 500 mg NS for PPIAN with addition of a mixture containing PVP, AG and Tween-80.

Placebo sample pastes were produced from arabinogalactan and potato starch.

For a comparative assessment of the activity, we used injectable Ivermec® (Nita-Pharm, Samara, Russia) containing 10 mg ivermectin and 40 mg tocopherol acetate per millilitre.

Concentration study

High-performance liquid chromatography (HPLC) method (15) was used to determine the concentration of IVM, ALB, and NS in products (analysis error = ±3%).

Parasiticidal activity of drugs

Randomized control-test study was performed in accordance with the guidelines for the preclinical study of new pharmacological substances (16) and European Convention for the Protection of Vertebrate Animals used for experimental and other scientific purposes (17).

Field trials were carried out from May to October 2021 on horses kept in the Experimental Station of Altai Experimental Agriculture, Altai Republic, Russia and Ltd. "Strelets" of the Shebalinsky district.

Selection of experimental horses

Adult horses of the Novoaltai breed weighing 450–500 kg (n = 151) were preselected for the experiments. The number of helminths eggs (strongyle, *Parascaris*, *Anoplocephala*) in 1 g of faeces was determined with Kotelnikov-Khrenov's method using a VIGIS counting chamber (18). Species differentiation of helminths was carried out on the basis of morphological and morphometrical features of the eggs and/or their larvae (19). For specific diagnosis of the strongyles, the faeces were subjected to coproculture followed by Baermann-

Orlov's larvascopic method and then the larvae were identified morphologically (20).

Horses naturally infected with strongyles (>150 egg per gram of faeces, EPG), *Parascaris* (>20 EPG) and *Anoplocephala* (>10 EPG) were selected for the experiment (21). During the experiment, horses were kept indoors and fed manually with standard diets (22). Selected horses with a similar degree of infection with helminths were randomly formed into experimental groups and faecal egg count reduction test (FECRT) was performed 14 days after the administration of the drugs (17).

Experiments

All experiments were performed in accordance with WAAVP guidelines (21). Four experiments were carried out (see below) within which, according to the principle of analogues (16), 7–16 experimental horses and 10–20 control horses were formed. Antiparasitic pastes (1–2 gram per 50 kilogram bodyweight, BW) were orally fed to the horses between 8–10 a.m.

i) In the first experiment, the horses (10 experimental and 10 control) were given 1 g / 50 kg BW of PPIA-1 product, 0.2 mg/kg IVM + 10 mg/kg ALB.

ii) In the second experiment, the horses (16 experimental and 20 control) were given 1 g / 50 kg BW of PPIAN product, containing 0.2 mg/kg IVM + 10 mg/kg ALB + 10 mg/kg NS.

iii) In the third experiment, horses (60 experimental and 12 control) were administered 3 samples of pastes:

PPIA-2-1: 1 g / 50 kg BW = IVM 0.2, ALB 1.0 mg / kg BW

PPIA-2-3: 1.5 g / 50 kg BW = IVM 0.2, ALB 3.0 mg / kg BW

PPIA-2-5: 2.0 g / 50 kg BW = IVM 0.2, ALB 5.0 mg / kg BW

Control - placebo 1 g / 50 kg BW.

iv) In the fourth experiment, horses (7 experimental and 16 control) were injected subcutaneously with Ivermec® (0.2 mg / kg BW). Control-placebo was sterile physiological saline in the same volume.

Post-treatment clinical and parasitological examinations

Body temperature, pulse rate, respiratory rate and general behavior of individual animals (e.g. nervousness) were assessed prior to and days 1 and 2 after the administration of drugs according to the method of veterinary clinical laboratory diagnostics (17).

The effectiveness of the drugs was evaluated 14 days after the treatment by counting the eggs in the faecal samples of experimental and control groups of animals based on the calculation of effectiveness indicators (25):

EI % = the proportion of infected animals;

EE % = the proportion of animals freed from parasites in relation to the untreated control animals;

IE %= decrease in the arithmetic mean number of eggs of the experimental groups in relation to the control;

Ef % = decrease in the geometric mean number of eggs of the experimental groups in relation to the control.

Statistical analyses

To compare the parasiticidal efficacy of the paste compositions, statistical analysis of data on the geometric mean value of the number of eggs of parasites was carried out. The parametric *t*-test was used to compare differences between the experimental and control groups of animals at a significance level of $P \leq 0.05$. Calculations were performed using the SAS/STAT® software Version 9.

Results

Solubility of the formulations

The change in the solubility of substances ALB, NS and IVM in their SD is presented in Tables 2–4. The maximum increase in the solubility of substances depended on the nature

of the substances, polymers and the time of mechanical processing:

i) The optimal increase in the solubility of ALB reached a value of 17.3 times in its SD of the composition of ALB:AG (1:9) at 6 hours. A further increase in the time of mechanical processing up to 7 hours did not lead to a significant increase in the solubility (only 17.4 times).

ii) The optimal increase in the solubility of NS reached a value of 7.9 times in its SD of the composition NS:PVP (1:9) at 6 hours. A further increase in the mechanical treatment time to 7 hours did not lead to a significant increase the solubility (only 8.0 times).

iii) The optimal increase in the solubility of IVM reached a value of 26.6 times in its SD of the composition of IVM:AG (1:9) at 6 hours. A further increase in the mechanical treatment time up to 7 hours did not lead to a significant increase in the solubility (only 26.7 times).

Table 2: Dynamics of changes in the solubility of albendazole in its solid dispersions with arabinogalactan within increasing machining treatment (m/t)

Compound	***Water solubility***	
	Absolute (mg/L)	**Increased (times)**
ALB (initial substance)	1.0	–
SD of composition ALB:AG (1:9) after 15 min m/t	2.1	2.1
SD of composition ALB:AG (1:9) after 2 h m/t	3.4	3.4
SD of composition ALB:AG (1:9) after 4 h m/t	15.7	15.7
SD of composition ALB:AG (1:9) after 6 h m/t	17.3	17.3
SD of composition ALB:AG (1:9) after 7 h m/t	17.4	17.4

SD = solid dispersions, ALB=albendazole, AG=arabinogalactan

Table 3: Dynamics of changes in the solubility of niclosamide in its solid dispersions with polyvinylpyrrolidone within increasing machining treatment (m/t)

Compound	***Water solubility***	
	Absolute (mg/L)	**Increased (times)**
NS (initial substance)	5.0	–
SD of composition NS:PVP (1:9) after 1h m/t	22.2	4.4
SD of composition NS:PVP (1:9) after 2 h m/t	29.5	5.9
SD of composition NS:PVP (1:9) after 4 h m/t	36.6	7.3
SD of composition NS:PVP (1:9) after 6 h m/t	39.7	7.9
SD of composition NS:PVP (1:9) after 7 h m/t	39.9	8.0

SD = solid dispersions, NS=niclosamide, PVP= polyvinylpyrrolidone

Clinical data

After feeding antiparasitic pastes, the clinical parameters of the animals remained within the physiological range.

Parasitological data

Preliminary coproscopy examinations revealed that the helminthic complex of horses is mainly represented by strongyles of the gastrointestinal tract (*Strongylus edentatus, S. equinus, S. vulgaris* and species of the genus *Trichonema*), *Parascaris* spp. and *Anoplocephala perfoliata*.

The results of testing drugs for strongyles infections indicated a very high (100%) parasiticidal activity of pastes PPIA-1, PPIA, PPIA-2-3 and PPIA-2-5. At the same time, pastes based on the initial active substances and the injection of ivermectin showed less efficiency (Ef = 22.5–49.8%) (Table 5).

Table 4: Dynamics of changes in the solubility of ivermectin in its solid dispersions with arabinogalactan within increasing machining treatment (m/t)

Compound	*Water solubility*	
	Absolute (mg/L)	**Increased (times)**
IVM (initial substance)	4.0	-
SD of composition IVM:AG (1:9) after 1h m/t	21.6	5.4
SD of composition IVM:AG (1:9) after 2h m/t	49.2	12.3
SD of composition IVM:AG (1:9) after 4h m/t	79.1	19.8
SD of composition IVM:AG (1:9) after 6h m/t	106.3	26.6
SD of composition IVM:AG (1:9) after 7h m/t	106.9	26.7

SD = solid dispersions, IVM=ivermectin, AG=arabinogalactan

Similarly, higher activity (100%) in the case of parascarosis was observed in comparison with the pastes with the initial substances (Ef = 23.3 and 41.8%) (Table 6).

In regards to anoplocephalidosis, PPIAN, PPIA-2-3, and PPIA-2-5 showed high activity (100%). While the paste containing IVM was not active, the product with ABZ significantly reduced EPG and the EE index was 78.6% (Table 7).

Table 5: Efficacy of produced antiparasitic drugs in combating equine strongylosis

Experiment number / group of animals	*Test product*	*Dose (mg of active substance /kg BW)*	*Number of horses in group*	*% infected*	*EPG[a] mean*	*EE[b] %*	*IE[c] %*	*Ef[d] %*	*P value[e]*
1 / Control	Placebo	–	10	100	252.5±40.7[f] 2.36±0.1	–	–	–	–
1 / Treatment	PPIA-1[g]	0.2 IVM[h] 10.0 ALB[i]	10	0.0	0 0	100.0	100.0	100.0	NA[j]
2 / Control	Placebo	–	20	75.0	167.2±28.1 2.31±0.08	–	–	–	–
2 / Treatment	PPIAN[k]	0.2 IVM 10.0 ALB 10.0 NS[l]	16	0.0	0 0	100.0	100.0	100.0	NA
3 / Control	Placebo	–	12	100	565.2±54.3 2.71±0.05	–	–	–	–
3 / Treatment	PPIA-2-1[m]	0.2 IVM 10.0 ALB	14	21.4	9.1±5.1 1.6±0.1	78.6	98.4	41.0	< 0.01
3 / Treatment	PPIA-2-3[n]	0.2 IVM 3.0 ALB	13	0.0	0 0	100.0	100.0	100.0	NA
3 / Treatment	PPIA-2-5[o]	0.2 IVM 5.0 ALB	11	0.0	0 0	100.0	100.0	100.0	NA
3 / Treatment	PPI-initial[p]	0.2 IVM	12	50.0	66.9±20.1 1.99±0.1	50.0	88.2	26.6	< 0.01
3 / Treatment	PPA-initial[q]	10.0 ALB	10	40.0	57.8±19.8 2.1±0.05	60.0	89.8	22.5	< 0.01
4 / Control	Placebo	–	16	100	464.3±95.6 2.51±0.08	–	–	–	–
4 / Treatment	Ivermec®	0.2 IVM	7	85.7	16.6±3.4 1.26±0.06	14.3	96.5	49.8	< 0.01

[a] EPG: egg per gram of faeces; [b]EE: the proportion of animals freed from parasites in relation to the untreated control animals; [c]IE: decrease in the arithmetic mean number of eggs of the experimental groups in relation to the control; [d]Ef: decrease in the geometric mean number of eggs of the experimental groups in relation to the control; [e] statistically significant at $P \leq 0.05$ when geometric means were compared to placebo; [f] The numerator is the arithmetic mean and the denominator is the geometric mean number of eggs; [g] 1 mL of PPIA-1 paste contained 10 mg of ivermectin and 500 mg of albendazole; [h] IVM: ivermectin; [i]ALB: albendazole; [j] NA: statistical analysis was not performed; [k] 1 mL of PPIAN paste contained 10 mg of IVM, 500 mg of ALB and 500 mg of niclosamide; [l] NS: niclosamide; [m] 1 mL of PPIA-2-1 paste contained 10 mg of IVM and 50 mg of ALB; [n] 1 mL of PPIA-2-3 paste contained 6.7 mg of IVM and 100 mg of ALB; [o] 1 mL of PPIA-2-5 paste contained 5 mg of IVM and 125 mg of ALB; [p] 1 mL of PPI-initial paste contained 10 mg of IVM; [q] 1 mL of PPA-initial paste contained 500 mg of ALB

Table 6: Efficacy of produced antiparasitic drugs in combating equine parascarosis

Experiment number / group of animals	*Test product*	*Dose (mg of active substance /kg BW)*	*Number of horses in group*	*% infected*	*EPG[a] mean*	*EE[b] %*	*IE[c] %*	*Ef[d] %*	*P value[e]*
1 / Control	Placebo	–	10	30.0	12.3±6.5*** 1.53±0.15	–	–	–	–
1 / Treatment	PPIA-1[g]	0.2 IVM[h] 10.0 ALB[i]	10	0.0	0 0	100	100	100	NA
2 / Control	Placebo	–	20	35.0	23.3±8.2 1.77±0.09	–	–	–	–
2 / Treatment	PPIAN[k]	0.2 IVM 10.0 ALB 10.0 NS[l]	16	0.0	0 0	100	100	100	NA
3 / Control	Placebo	–	12	25.0	7.9±4.5 1.46±0.08	–	–	–	–
3 / Treatment	PPIA-2-1[m]	0.2 IVM 10.0 ALB	14	14.3	0.68±0.5 0.67±0.05	42.8	91.4	54.1	< 0.05
3 / Treatment	PPIA-2-3[n]	0.2 IVM 3.0 ALB	13	0.0	0 0	100	100	100	NA
3 / Treatment	PPIA-2-5[o]	0.2 IVM 5.0 ALB	11	0.0	0 0	100	100	100	NA
3 / Treatment	PPI-initial[p]	0.2 IVM	12	16.6	2.9±2.4 1.12±0.2	33.6	63.3	23.3	> 0.05
3 / Treatment	PPA-initial[q]	10.0 ALB	10	20.0	0.73±0.6 0.85±0.03	20.0	90.8	41.8	< 0.05

[a-q] For the abbreviations see footnotes of Table 5

Table 7: Efficacy of produced antiparasitic drugs in combating equine anoplocephalidosis

Experiment number / group of animals	*Test product*	*Dose (mg of active substance /kg BW)*	*Number of horses in group*	*% infected*	*EPG[a] mean*	*EE[b] %*	*P value[e]*
2 / Control	Placebo	–	20	15.0	6.15±3.8[f] 1.35±0.16	–	–
2 / Treatment	PPIAN[k]	0.2 IVM 10.0 ALB 10.0 NS[l]	16	0.0	0 0	100	NA
3 / Control	Placebo	–	12	66.7	49.4±14.7 1.79±0.1	–	–
3 / Treatment	PPIA-2-1[m]	0.2 IVM 10.0 ALB	14	14.3	6.1±2.8 1.31±0.07	78.6	< 0.05
3 / Treatment	PPIA-2-3[n]	0.2 IVM 3.0 ALB	13	0.0	0 0	100	NA
3 / Treatment	PPIA-2-5[o]	0.2 IVM 5.0 ALB	11	0.0	0 0	100	NA
3 / Treatment	PPI-initial[p]	0.2 IVM	12	58.3	43.8±13.2 1.82±0.09	12.6	NA
3 / Treatment	PPA-initial[q]	10.0 ALB	10	30.0	8.9±5.4 0.92±0.17	78.6	< 0.05

[a-q] For the abbreviations see footnotes of Table 5.

Discussion

In the present study, innovative multicomponent anthelmintic formulations manufactured by solid dispersions of albendazole, ivermectin and niclosamide modified with mechanochemical technology namely "PPI-AN" and "PPIA-2-3" pastes showed 100% efficacy against nematodes (strongyles and *Parascaris*) and cestodes (*Anoplocephala*) of the gastrointestinal tract while original substances had lower efficacy in reduction of parasites eggs 14 days after treatment of naturally-infected horses. Similarly in a previous study, using the active substances of fenbendazole, triclabendazole and ivermectin, two-component antiparasitic drugs were developed in the form of solid dispersions, which formed supramolecular complexes in water. Those complexes were highly effective against the gastrointestinal strongylid nematodes, *Moniezia expansa* (cestodes) and *Dicrocoelium dendriticum* (trematodes) when administered orally to sheep (9). At the same time, the initial substances demonstrated significantly lower efficiency. The high parasiticidal activity of these preparations were explained by the increased values of solubility in water and bioavailability. Interestingly, a threefold decrease in the dosage of substances in medicinal compositions did not lead to decrease in their anthelmintic activity (9). In another study on sheep the resulting suspension concentrates based on albendazole and ivermectin conjugated with arabinogalactan polysaccharide were 5–10 times more effective than the therapeutic dose of the original substances in the reduction of eggs of gastrointestinal strongylids and *M. expansa* (10). In horses however, to date only two studies were performed albeit on a limited number of animals (20 and 40 horses), only with supramolecular complex of ivermectin, and only on strongyles and *Oxyuris equi* (7). It is known that mechanochemical modifications of antiparasitic compounds such as albendazole, fenbendazole and ivermectin increases their efficacy through different roots including increasing solubility, membrane permeability, and improved delivery of drug molecules to the active sites of appropriate receptors (9, 10). However, further studies are needed to characterize effectiveness pathways of herein presented formulations.

Results showed that mechanochemical solid-phase modification of therapeutic substances IVM, NS, and ALB treated with PVP and AG increased their solubility 8.0–26.7 times compared with original forms of substances NS, ALB and IVM. This technique which can be employed to design various forms of promising complex preparations with larger spectrum of activity increases the solubility and activity of preparations significantly (bioavailability) hence reduced doses of AI will be needed for antiparasitic treatments (23). Solid dispersions of mechanically modified substances of preparations in the form of aqueous suspensions have proven themselves well in the treatment of parasitic infections in other animals. For instance, in sheep the SDs obtained by mechanochemical modification of fenbendazole (FBZ) with arabinogalactan (AG) had 18 times more solubility and at a one-third dose (i.e. 3.0 mg/kg BW) showed 100% efficacy in treatment of dictyocaulosis, strongyloidiasis, and gastrointestinal strongylids infections, and 98.3% efficacy in trichurosis (24). In another study, antiparasitic compositions of SD based on FBZ, triclabendazole (TCB) and IVM with PVP showed high activity against strongylids, *Moniezia* and *Dicrocoelium* of sheep (25). In the latter work threefold decrease in the dosage of FBD and TCB did not lead to a decrease in the parasiticidal activity of the drugs (25).

All being said, further studies are needed to confirm whether formulated products with this technique will have more resistance in tar-

get tissues and subsequently reduced frequency of treatments are needed.

Conclusion

This study showed that solid-phase mechanochemical technology could be applied in equine anthelminthics production. Two formulated antiparasitic pastes presented herein namely "PPIAN" containing 0.2 mg ivermectin, 10.0 mg albendazole, 10.0 mg niclosamide and "PPIA-2-3" containing 0.2 mg ivermectin and 3.0 mg albendazole showed 100% efficacy against nematodes (strongyles and *Parascaris*) and cestodes (*Anoplocephala*). It is suggested that future studies focus on plasma concentration-time profile of these highly effective pastes.

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Conflict of interest

There was no conflict of interest to declare.

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