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ORIGINAL ARTICLE

Innovative anthelmintic based on mechanochemical technology and their efficacy against parasitic infection of sheeps

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ABSTRACT

Objective: Solubility and bioavailability are crucial for maximizing the activity of an antiparasitic drug. This study aimed to develop a combined preparation for antiparasitic medicines using ivermectin (Iver), fenbendazole (FBZ), and triclabendazole (TBZ), considering their solubility, bioavailability, and activity.

Materials and Methods: Innovative preparations in solid dispersions (SD) were obtained using the joint mechanical processing of drug substances with polyvinylpyrrolidone (PVP) in an LE-101 roller mill. The preparations' efficacy was studied in 140 sheep spontaneously infected with gastrointestinal Strongylata, *Dicrococelium dendriticum*, *Moniezia expansa*, and *Melophagus ovinus*. The preparations were given individually to the sheep in the form of an aqueous suspension orally. Their effectiveness was evaluated using intravital and postmortem parasitological examinations.

Results: The results confirmed the increase in solubility of substances by 13–29 times. The experiments have shown the high efficacy of SD composition of FBZ/Iver/PVP (1/1/9) containing FBZ (at 3.0 mg/kg *b/w*) and Iver (at 0.2 mg/kg *b/w*) when used against gastrointestinal Strongylates and *M. expansa* (95.8% and 100%, respectively), to a lesser extent against *M. ovinus* (38.5%). The SD composition of TBZ/Iver/PVP (1/1/9) of TBZ (at 3.0 mg/kg *b/w*) and Iver (at 0.2 mg/kg *b/w*) showed a high efficacy against gastrointestinal Strongylata and *D. dendriticum* (96.8% and 100%, respectively) and less activity against *M. ovinus* (61.6%).

Conclusion: The high parasiticidal activity of SD based on FBZ, TBZ, and Iver in comparison with initial substances is explained by the formation of inclusion complexes of these substances with PVP when SD is dissolved in water and the synergistic effect of the active substances of the preparations. The resulting complexes have increased solubility in water and bioavailability. The use of such an SD suggests a significant reduction in the dosages of FBZ and TBZ without losing parasiticidal activity.

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Fenbendazole; ivermectin; triclabendazole; parasitocidal activity; solid dispersions.

Introduction

The parasitic diseases of sheep in Gorny Altai are characterized by a great variety and are represented by all the main invasions of nematodes, trematodes, cestodosamias, and arachnoentomoses. In various natural provinces, animals have formed a parasitic complex, requiring different approaches when carrying out antiparasitic measures and therapeutic agent choice [1].

In industrial practice, it is often necessary to simultaneously control a wide range of parasitic infestations. Several classes of zooparasites represent the causative agents. However, there are very few highly effective therapeutic agents available. The parasitic complex of sheep developed in various natural provinces implies using at least two new complex antiparasitic preparations with a broad spectrum of action, convenience, and availability for practical use [2].

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The technology of branch management (distant sheep breeding) practiced in Gorny Altai naturally presupposes minimizing interference with the parasitic system. It is carried out by reducing the number of treatments and attracting drugs with a broad spectrum of action into the system of antiparasitic measures [3].

Innovative antiparasitic drugs have been developed and proposed for veterinary practice, having a broad spectrum of action against several animal parasites. These drugs were based on anthelmintics from the class of macrocyclic lactones with high activity against nematodes and ectoparasites of animals [4]. Another promising anthelmintics class is benzimidazoles, which are active against a wide range of helminths [5,6]. In this regard, a rational combination of these drugs is needed, making it possible to effectively control a wide range of parasites. Therefore, we have chosen ivermectin (Iver), having nematicidal and entomocidal actions, fenbendazole (FBZ), having nematicidal and insecticidal activities, and triclabendazole (TBZ), which is a well-known anti-fluke drug. These are sometimes used in animals with higher doses due to their low solubility in water; these drugs cannot show their usual activities. The increase in solubility can be ensured by the joint mechanical treatment with water-soluble polymers, particularly with polyvinylpyrrolidone (PVP). This approach was previously applied to benzimidazole substances [7,8]. Solid dispersions (SD) were obtained in visible nanodispersed powders which formed supramolecular complexes in water with increased solubility, bioavailability, and efficiency. This work aims to develop innovative combined drugs using the mechanochemical methods to improve the solubility of Iver, FBZ, and TBZ during joint machining with PVP, and the antiparasitic activities of the obtained preparations were assessed in sheep.

Materials and Methods

Ethical statement

The experiments were carried out according to the "control test" principle. According to analogs' principle, the sheep were selected, and experimental and control groups of animals (placebo control) were randomly formed. The study was carried out following the guidelines for the experimental (preclinical) research of new pharmacological substances [9] and the rules adopted by the European Convention [10].

Chemicals

The following substances were used:

a) Iver, manufactured by Shandong Qilu King-Phar Pharmaceutical Co. Ltd., China;
b) FBZ. manufactured by Renzin Chemicals Ltd., China;
c) TBZ, manufactured by Sigma-Aldrich;
d) PVP, manufactured by Boai NKY Pharmaceuticals Ltd., China.

Machining of FBZ (or TBZ) substances and the polymer was carried out at their weight ratio of 1:9 at LE-101 roller mill (Hungary) following the methods described previously [8]. SD of FBZ/PVP (1/9) compositions (abbreviated FP) were obtained, TBZ/PVP (1/9) (abbreviated as TP). When the calculated amount of Iver was added to the above compositions of drugs with PVP, and the stoichiometry of the 1/1/9 composition was observed, the SD composition of FBZ/Iver/PVP (1/1/9) (abbreviated as FIP), TBZ/Iver/PVP (1/1/9) (abbreviated as TIP). These FIP and TIP formed stable aqueous suspension, which is ready for the treatment of sheep.

Helminthiasis sheep

The analysis of the drugs' antiparasitic activity was carried out in 2018 at a sheep farm of the Altai Republic during the maximum infection of animals. The experiment used 140 6–8-month-old sheep of the Altai breed weighing 25–30 kg. The sheep were spontaneously infected with gastrointestinal strongylates, dicrocelia (*Dicrococelium dendriticum*), *Moniezia expansa*, and sheep ked (*Melophagus ovinus* L.). During the experiments, the sheep were not grazed and kept indoors, and fed according to the norms and rations for feeding livestock [11].

Feces were studied according to the McMaster method [12] 3 days before the experiment. Sheep were randomly assigned to experimental groups to determine further the geometric mean number of eggs per gram of feces [13,14]. From the number of sheep infected with *Moniezia*, revealed by ovoscopic studies of feces, experimental and control groups of sheep were formed to conduct experiments with a postmortem examination of the intestines and to calculate the geometric mean of the imaginal forms of helminths.

Sheep melophagosis

The assessment of the preparations' activity was carried out on the same groups of animals as in the study of the effectiveness in helminthiasis. All animals were examined for contamination with adult forms of sheep ked. When examining the rune of sheep, dead parasites were not taken into account. Based on the survey results, the geometric mean of the number of sheep ked in animals was determined.

Experimental groups

The experimental sheep were divided into three series of experiments. In two series, in which ovoscopic studies of feces were carried out, four experimental groups of 10 animals each and one control group of 20 animals were

formed. In the third series, with postmortem helminthological examinations in moniesiasis, four experimental and one control group of animals, four heads each, were included. In the first and third series of experiments, FIPs were tested. In the second series, TIPs were tested in low dosages for the active substances of benzimidazoles. Antiparasitic compositions based on SD preparations were administered orally to animals of the experimental groups. The experimental sheep were fed with 5% aqueous suspensions of antiparasitic drugs in dosages of FBZ (at 1–3 mg/kg *b/w*) and TBZ (at 2 and 3 mg/kg *b/w*) of the active substance and Iver (at 0.2 mg/kg *b/w*).

Animal treatments

Before setting up the experiments, the animals were weighed and microchipped. Stool samples for ovoscopic studies were taken from the rectum of sheep. The drugs' effectiveness was determined according to coproovoscopic examinations after administering drugs on day 15 (nematodes) and day 30 (Dicrococelium). The efficacy of drugs against imaginal forms of *Moniezia* was determined 10 days after deworming by opening the small intestine and counting scolexes and fragments of strobil cestodes. The effectiveness of samples of parasiticides against sheep bloodsuckers was determined 15 days after giving the drug by examining the fleece of sheep to calculate the number of living parasites' geometric mean values [14]. Before the experiments, after days 1, 3, and 5 of drinking the preparations, the animals' physiological parameters (body temperature, pulse rate, respiration, and scar movement) were recorded [15].

Statistical analysis

The parasiticidal activity of the preparations (Ef,%) was calculated as a decrease (in%) in the geometric mean values of the number of eggs of helminths or parasitic groups to the control (not treated). A statistical analysis of the number of helminth eggs or imaginal forms of parasites was carried out to compare the parasiticidal activity. To reach the differences between the experimental and control groups of animals, a parametric *t*-test was used at a significance level of $p \leq 0.05$. The calculations were performed using the SAS/Stat software for Windows.

Results

An important indicator for assessing the effectiveness of mechanical treatment of drug substances with polymers is increased water solubility, indicating specific changes in the resulting drugs' physicochemical parameters. In our experiments, the analysis of the solubility of the obtained SD of FBZ and TBZ with PVP showed an increase in solubility by 13–29 times, which, as expected, should have affected the antiparasitic activity of the prepared SD (Table 1). The data of Table 1 showed that even a mixture without mechanical treatment has a higher solubility value. It was

Table 1. The solubility in water of initial substances and their compositions.

No	Samples, conditions of preparation	Solubility	
		Absolute, mg/l	Increase, multiplicity
	Compositions based on FBZ		
1	FBZ- initial sample	0.33	–
2	Physical mixture (PM) of FBZ/PVP (1/9), without M[a]	0.67	2
3	SD of FBZ/PVP (1/9), 2 h M	2.0	6
4	SD of FBZ/PVP (1/9), 4 h M	2.70	8
5	SD of FBZ/PVP (1/9), 8 h M	4.50	13
6	SD of FBZ/PVP (1/9), 16 h M	4.60	14
7	SD of FBZ/PVP (1/9), 20 h M	4.60	14
	Compositions based on TBZ		
8	TBZ -initial sample	2.0	–
9	PM of TBZ/PVP (1/9) without M[a]	2.30	1
10	SD of TBZ/PVP (1/9) , 2 h M	11.60	4
11	SD of TBZ/PVP (1/9), 4 h M	18.10	9
12	SD of TBZ/PVP (1/9), 8 h M	34.50	17
13	SD of TBZ/PVP (1/9), 16 h M	57.60	29
14	SD of TBZ/PVP (1/9), 20 h M	57.10	29

[a]M = machining.

possible because of the solubilizing properties of a hydrophilic polymer (PVP). After the mechanical treatment of FBZ and PVP (in the ratio of 1:9) SD was obtained, and it had a significant increase in solubility. The increasing time in mechanical treatment (more than 8 h) does not lead to a corresponding rise in SD's solubility. Therefore, the optimal time to obtain the target product – SD composition FBZ/PVP (1/9) – is chosen as 8 h.

When machining TBZ composites with PVP, the same pattern is observed in an increase in solubility with an increase in machining time. Optimal time for taking the soluble SD of the TBZ/PVP (1/9) composition is at least 16 h of mechanical treatment, which is probably due to the peculiarities of the physicochemical properties of the TBZ substance.

During clinical studies, no harmful effects of antiparasitic drugs on animal health were identified. All clinical parameters did not deviate from physiological norms. In a series of experiments with FIP, sheep of the control group were infected with gastrointestinal Strongylates by 85.0% with a geometric mean of 2.9 eggs per gram of feces (e/g.f.). In a series of TIP experiments, sheep were infected with helminths by 80.0% with a geometric mean of 2.69 e/g.f. (Table 2).

Testing FIP against gastrointestinal Strongylates (Table 2) showed the efficiency indicator as 100%, and the FP compositions at 2 and 3 mg/kg *b/w* (No. 3 and 4) showed relatively high activity (Ef were 62.8% and 92.1%, respectively). Substance FBZ (No. 5 in the dosage 3.0 mg/kg *b/w*) turned out to be insufficiently active (17.3%). TIP composition (No. 7) showed a high activity of 95.6%. On the contrary, the TP compositions (No. 8 and 9) and the TBZ substance (No. 10) showed no activity against these helminths.

Due to the peculiarities of the isolation of eggs *Moniezia* spp. with feces and significant dispersion of their indicators in samples, according to the results of ovoscopy, we can only judge the qualitative side of the effect of drugs on parasites. Experiments considering the imaginal forms of parasites in sheep's intestines allow one to evaluate the effectiveness of drugs against *Moniezia* more accurately. Table 3 presents the statistical indicators of geometric mean values of the number of eggs in sheep feces samples when exposed to parasiticides against *Moniezia* spp.

In experiments, when assessing the activity of the compositions FBZ and Iver against *Moniezia* spp. control sheep are infected by 30.0% with a geometric mean of 3.10 eggs per gram of feces (e/gm.f.). In the experiments with TBZ and Iver, control sheep were infected with *Moniezia* by 25.0% with 2.90 e/gm.f. (Table 3).

Experiments carried out indicate that the FIP and FP compositions (No. 2 and 4) significantly reduce *Moniezia* spp. eggs in feces samples, at the same time, the initial substance FBZ (No. 5), at 3.0 mg/kg *b/w*, does not have a good effect on the number of eggs. All compositions TBZ and the initial preparation did not significantly affect the number of eggs in the samples of experimental animals (No. 12–15).

In an experiment with FBZ compositions, when examining the intestines of four sheep of the control group, it was found that all animals were infected with *M. expansa* with a geometric mean of the number of helminths of 3.6. Efficacy of FP formulations at 1 and 2 mg/kg *b/w* (Table 3) was, respectively, 55.9% and 83.5%, at 3.0 mg/kg *b/w* obtained

Table 2. Efficacy of parasiticides in sheep against gastrointestinal strongylates.

No	Groupofanimals	Samples of parasiticides for tests	Dose, mg of AS / kg of *b/w*	Number of sheep in group	Geometric mean number of eggs/gm feces	Efficacy (Ef), %	*p*-value
			Tests of preparation based on FBZ				
1	Control	Placebo	–	20	2.90	–	–
2	Treatment	FIP	Iver – 0.2, FBZ – 3.0	10	0	100	NA[a]
3	Treatment	FP	FBZ – 2.0	10	1.08	62.8	< 0.001
4	Treatment	FP	FBZ – 3.0	10	0.23	92.1	< 0.001
5	Treatment	FBZ- substance	FBZ – 3.0	10	2.40	17.3	> 0.05
			Tests of preparation based on TBZ				
6	Control	Placebo	–	20	2.69	–	–
7	Treatment	TIP	Iver – 0.2, TBZ – 3.0	10	0.12	95.6	< 0.001
8	Treatment	TP	TBZ – 2.0	10	2.65	0	NA
9	Treatment	TP	TBZ – 3.0	10	2.70	0	NA
10	Treatment	TBZ-substance	TBZ – 3.0	10	2.70	0	NA

[a]NA = not analyzed.

Table 3. Statistical indicators of the number of eggs and helminths when exposed to parasiticides against *Moniezia* spp.

No	Group of animals	Samples of parasiticides for tests	Dose, mg of AS / kg *b/w*	Number of sheep in group	Geometric mean meaning indicators	Efficacy (Ef), %	*p*-value
Tests of preparation based on FBZ (Ovoscopy, Geometric mean number of eggs/gm feces)							
1	Control	Placebo	–	20	3.10	–	–
2	Treatment	FIP	Iver – 0.2 FBZ – 3.0	10	1.10	–	<0.001
3	Treatment	FP	FBZ – 2.0	10	2.18	–	<0.01
4	Treatment	FP	FBZ – 3.0	10	1.65	–	<0.001
5	Treatment	FBZ substance	FBZ – 3.0	10	2.90	–	> 0.05
Postmortem helminthoscopy (Geometric mean number of helminths, ind.)							
6	Control	Placebo	–	4	3.60	–	–
7	Treatment	FP	FBZ – 1.0	4	1.59	55.9	< 0.01
8	Treatment	FP	FBZ – 2.0	4	0.59	83.5	< 0.01
9	Treatment	FP	FBZ – 3.0	4	0	100	NA
10	Treatment	FBZ substance	FBZ – 3.0	4	1.41	60.7	< 0.01
Tests of preparation based on TBZ (Ovoscopy, Geometric mean number of eggs/gm feces)							
11	Control	Placebo	–	20	2.90	–	–
12	Treatment	TIP	Iver – 0.2 TBZ – 3.0	10	2.70	-	> 0.05
13	Treatment	TP	TBZ – 2.0	10	2.75	-	> 0.05
14	Treatment	TP	TBZ – 3.0	10	2.80	-	> 0.05
15	Treatment	TBZ substance	TBZ – 3.0	10	2.80	-	> 0.05

100% efficiency (no. 9). Substance FBZ (No. 10) turned out to be less active, with an indicator of 60.7%.

When studying the activity of FBZ compositions against *D. dendriticum*, the control group of animals was infected by 45.0% with 1.90 eggs per gram of feces; in experiments with compositions of TBZ, sheep in the control group were infected by 40.0% with an identical indicator of the number of eggs (Table 4).

The effectiveness of FIP and FP against *D. dendriticum* was 5.3–10.6. The starting substance FBZ (Table 4) also did not show sufficient activity at 5.3%. The TIP composition against *D. dendriticum* was quite active (99.9%), while TP at 2 mg/kg *b/w*. (No. 8) showed 60%, and at 3.0 mg/kg *b/w* (No. 9) it showed 100% activity. Substance TBZ (No.10) against *D. dendriticum* was not active enough; the efficacy rate was only 21.1%.

When assessing the effectiveness of FIP against *M. ovinus*, sheep in the control group were infested with parasites by 95.0%, with a geometric mean of 1.30 ind. per animal. The other control group animals have been infected by 90.0% with a geometric mean of 1.30 ind. sheep ked per sheep (Table 5).

When testing the activity of FIP against *M. ovinus* (Table 5) in the experimental group, the efficiency indicator was 38.5%. Still, FP and FBZ substances (No. 3 and 4) were not effective (0% and 7.7%). The composition TIP against *M. ovinus* showed a higher activity (61.6%), TP and substance TBZ (No. 7 and 8) in the experiment did not demonstrate activity (0%). Only SD compositions containing Iver were active against *M. ovinus*.

Discussion

In the Altai Mountain farms, sheep are parasitized by a wide range of infectious diseases pathogens; the dominant position is occupied by nematodes of the Strongylata suborder, helminths of the genera *Moniezia*, and *Dicrococelium* are represented mainly. Among the parasitic insects, the most representative is the sheep's bot fly and sheep ked. For effective control of all these complex parasites, it is necessary to involve drugs with a broad spectrum of activity against various classes of helminths and parasitic arthropods in the system of measures. The use of such complex drugs allows reducing the frequency of use and consumption of antiparasitic drugs, without damage in an epizootic situation for invasive diseases, which served as the motivation for this study.

In the experiments carried out, the preparations obtained by the methods of mechanical processing of the FBZ, TBZ, Iver substances with PVP were tested. It is known that in recommended doses, Iver is highly effective and has a broad parasiticidal spectrum against nematodes

Table 4. The effectiveness of parasiticides against *D. dendriticum.*

No	Group of animals	Samples of parasiticides for tests	Dose, mg of AS/ kg of *b/w*	Number of sheep in group	Geometric mean number of eggs/gm feces	Efficacy (Ef), %	*p*-Value
			Tests of preparation based on FBZ				
1	Control	Placebo	–	20	1.90	–	–
2	Treatment	FIP	Iver – 0.2 FBZ – 3.0	10	1.80	5.3	> 0.05
3	Treatment	FP	FBZ – 2.0	10	1.75	7.9	> 0.05
4	Treatment	FP	FBZ – 3.0	10	1.70	10.6	> 0.05
5	Treatment	FBZ substance	FBZ – 3.0	10	1.80	5.3	> 0.05
			Tests of preparation based on TBZ				
6	Control	Placebo	–	20	1.90	–	–
7	Treatment	TIP	Iver – 0.2 TBZ – 3.0	10	0.04	99.9	< 0.001
8	Treatment	TP	TBZ – 2.0	10	0.76	60.0	< 0.001
9	Treatment	TP	TBZ – 3.0	10	0	100	NA
10	Treatment	TBZ-substance	TBZ – 3.0	10	1.50	21.1	> 0.05

Table 5. The effectiveness of parasiticides against *M. ovinus.*

No	Group of animals	Samples of parasiticides for tests	Dose, mg of AS / kg of *b/w*	Number of sheep in group	Geometric mean the number of parasites on the animal, ind.	Efficacy (Ef), %	*p*-value
			Tests of preparation based on FBZ				
1	Control	Placebo	–	20	1.30	–	–
2	Treatment	FIP	Iver – 0.2 FBZ – 3.0	10	0.80	38.5	>0.05
3	Treatment	FP	FBZ – 3.0	10	1.30	0	NA
4	Treatment	FBZ substance	FBZ – 3.0	10	1.20	7.7	> 0.05
			Tests of preparation based on TBZ				
5	Control	Placebo	–	20	1.30	–	–
6	Treatment	TIP	Iver – 0.2 TBZ – 3.0	10	0.50	61.6	> 0.05
7	Treatment	TP	TBZ – 3.0	10	1.30	0	NA
8	Treatment	TBZ substance	TBZ – 3.0	10	1.40	0	NA

mites and insects, FBZ against nematodes and cestodes, TBZ against trematodes [16–18]. The above-mentioned antiparasitic substances after joint mechanical treatment with polymers gives the possibility to obtain SD with significantly increase the solubility of these substances. SDs of drugs are considered delivery systems for these substances and improve the solubility, bioavailability, etc. [19,20].

The minimum regulated doses of FBZ and TBZ for oral administration in various sheep helminthiases are 10 mg/kg *b/w* [5]. In the experiments, the doses of FBZ and TBZ reduced by more than three times in SD with PVP showing relatively high efficiency for helminthiases. The composition FIP was highly effective against gastrointestinal Strongylata (Ef 100%), against *M. ovinus* (Ef 38.5%) and ineffective against *D. dendriticum*. More than that, FP at 3 mg/kg *b/w* was quite active against gastrointestinal Strongylata and *Moniezia benedeni* (Ef = 92.1% and 100%, respectively) but not active against *D. dendriticum* and *M. ovinus*.

Composition TIP showed high efficacy against gastrointestinal Strongylata (effect of Iver) and *D. dendriticum* (Ef = 95.6% and 99.9%, respectively). It was less effective against *M. expansa* and *M. ovinus* (Ef = 64.5% and 61.6%, respectively). TP was highly effective against *D. dendriticum* (100%) but not active against gastrointestinal Strongylata, *M. expansa*, and *M. ovinus*. In all experiments, the initial substances FBZ and TBZ showed significantly less activity.

Other scientists showed similar results on the assessment of the activity of mechanically modified preparations for other benzimidazoles:

The efficacy of a supramolecular complex based on albendazole and TBZ against the nematodes of the digestive tract and *Fasciola* spp. in sheep was studied, at therapeutic doses of 5.0 mg/kg, and the drug showed 100% effectiveness [21].

The supramolecular complex of FBZ and PVP in doses of 1–3 mg/kg *b/w* with oral administration of the drug was shown to be highly effective against intestinal helminths of sheep (94%–100%). In comparison, FBZ substance at 10 mg/kg *b/w* showed 95.6%–100% efficacy, and at 1.0 mg/kg *b/w* was practically ineffective [22]. Moreover, the complex showed 97.3% efficacy at 2 mg/kg *b/w* against *Moniezia* spp. infection of sheep [23].

The complex based on FBZ and PVP with the addition of 1%–2% NaDSS (sodium dioctyl sulfosuccinate) is highly effective in doses of AS of 2.0 and 3.0 mg/kg *b/w* (92.4%–100%) against gastrointestinal Strongylata and *M. expansa* in sheep [24].

The complex of TBZ and arabinogalactan has 100% efficacy in cattle fascioliasis at 2.5 mg/kg *b/w* [19].

It can be concluded that complex antiparasitic drugs were first obtained by solid-phase modification of FBZ, TBZ, and Iver with PVP. The developed preparations based on SD of these substances showed high activity against nematodes of the suborder Strongylata, Strongylates of the gastrointestinal tract, *M. expansa*, and *D. dendriticum* in sheep and significantly reduced the number of *M. ovinus*.

The obtained samples of preparations are fine beige powders in the form of a dry concentrate of a suspension, which forms a suspension ready for water use. The use of these complex compositions will allow sufficient control of sheep infestation by the major parasitic invasions in the mountainous areas of Western Siberia.

Conclusion

Experiments have shown the high efficacy of FIP at FBZ of 3.0; Iver at 0.2 mg/kg *b/w* when administered orally against nematodes of the suborder Strongylata, *M. expansa*, and *Melophagus ovinus*. Composition of TIP at TBZ of 3.0 and Iver at 0.2 mg/kg *b/w* showed high efficacy against gastrointestinal Strongylata and *D. dendriticum* and was not effective against *M. expansa*. The parent substances FBZ and TBZ demonstrated a significantly lower efficacy in sheep helminthiasis. The high parasiticidal activity of the studied compositions is explained by increased solubility in water and bioavailability. A threefold decrease in the dosage of FBZ and TBZ in drug compositions did not lead to a decrease in their anthelminthic activity.

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Conflict of interest

There is no conflict of interest to declare.

Authors' contribution

Prof. Marchenko Victor A. designed, organized the experiments, participated in the processing of materials, and writing of the article, and also took part in a critical review of the manuscript. Prof. Khalikov Salavat S. studied mechanochemical modification of the substances FBZ, TBZ, and Iver using PVP. Received, evaluated the quality of SD, prepared the preparations for testing, and also took part in the manuscript's preparation and design. Dr. Vasilenko Yury A. conducted experiments and coprooscopic studies. Dr. Ilyin Mikhail M. carried out the HPLC analysis of the obtained compositions and assessment of changes in their solubility. Dr. Kravchenko Irina A. conducted coproovoscopic examinations, analysis of research materials, and manuscript preparation.

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