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Research Article

ANALYSIS OF ALBENDAZOLE COMPLEXES AND EFFECTS ON HELMINTHS

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ABSTRACT

The article describes the results of obtaining supramolecular complexes of albendazole with glycyrrhizic acid and monocalic salts in various molar ratios, studying their chemical structure by various physicochemical methods and studying the anthelmintic properties of the obtained supramolecular complexes.

KEYWORDS

Albendazole, glycyrrhizic acid, supramolecular complex, liquefaction temperature, ultraviolet spectrum, infrared spectrum, pharmaceutical leech, helminths.

INTRODUCTION

At present, one of the main obstacles in the implementation of agrarian reforms aimed at better meeting the needs of the population of the republic for cheap and high-quality food products is a number of

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livestock diseases, including helminthiasis of small ruminants. The methods of infecting animals with helminths differ in that helminths enter the body through food and water containing helminth eggs, larvae, or through the skin of animals. Helminthiasis is often transmitted from a sick animal to its unborn child. Nematode larvae easily penetrate the stem or root of most plants. As a result of helminthiasis, the productivity of animals, the growth rate of plants is reduced and, as a result, animals and plants die. This, in turn, causes great economic damage to the national economy. Trematodes are usually common in agriculture and domestic animals: fascioliasis, orientobilharzia, dicroceliosis; from cestodosis: moniesiosis, tyzantseziosis, avitellinosis, echinococcosis, coenurosis; from nematodosis: fascioliosis, orientobilharzia, dichroseliasis; moniesiosis, tysancesiosis, avitellinosis, echinococcosis, coenurosis; ascariasis and ascaridiosis, parascariasis, oxyurosis, hemonchosis, nematodirosis, habertiosis, dictyocaulosis, oxyurosis, hemangiomas, nematodirosis, habertiosis, dictyocaulosis, protostrongylids. In addition, the parasitizing effect of more than 1000 helminths on vertebrates has been revealed [1,2].

The use of local remedies for helminthiasis of livestock and poultry, the localization of foreign drugs, and the preparation and use of water-soluble forms of albendazole complexes that resist the action of helminthiasis in sheep remain relevant.

MATERIALS AND METHODS

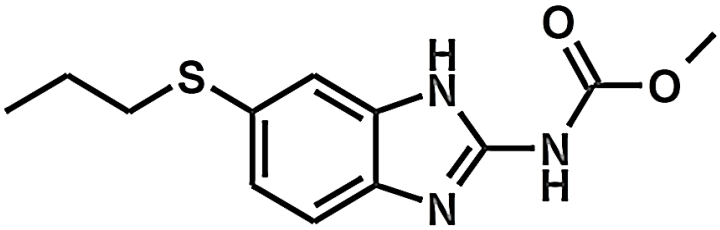
Meat, dairy and leather products obtained from large and small horned animals are important for the daily needs of the population. The quality of products naturally decreases due to the fact that animals are affected by various parasitic diseases [3].

One of the most important symptoms of helminthiasis is a decrease in the body's immunity. Such organisms are also responsible for other diseases.

As a result of many years of research by our domestic helminthologists, 88 types of free worm helminth diseases were discovered in sheep (7 types of trematodes, 11 types of cestodes, 77 types of nematodes). 48 species of helminth diseases have been found in goats, 55 species in cattle, 25 species in camels, 53 species in horses, 25 species in donkeys, 25 species in pigs, 32 species in dogs and 19 species in cats. [4].

Today, as a precautionary measure against helminthic diseases, solutions of alkazan 10%, albaza 11.36%, envir, alvet, clozatrem, ricazole and other chemicals are used. [5]. In the drugs listed above, the anthelmintic drug albendazole is considered more effective.

Albendazole (ABZ) is a chemical compound with anthelmintic action that belongs to the group of benzimidazoles. General gross formula C12H15N3O2S. In IUPAC nomenclature, [5-(propylthio)-1H-benzimidazol-2-yl] carbamic acid is called methyl ester. The chemical structure of albendazole can be represented as follows:



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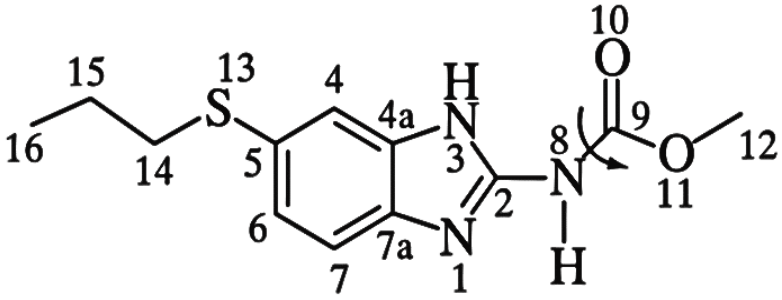
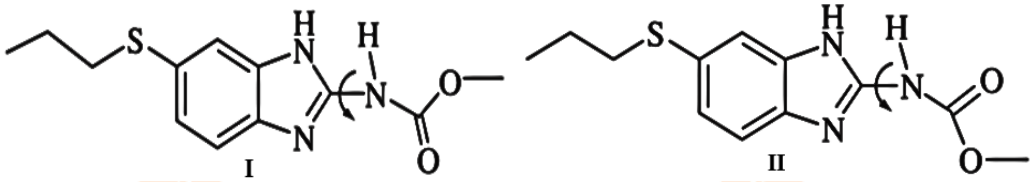
Albendazole is a white powdery substance. Dissolves in dimethyl sulfoxide and in strong acids and alkalis. Slightly soluble in methyl alcohol, in ethyl acetate, and also poorly soluble in chloroform, practically insoluble in water [6].

The order of the carbon atoms in the albendazole molecule can be represented as follows:

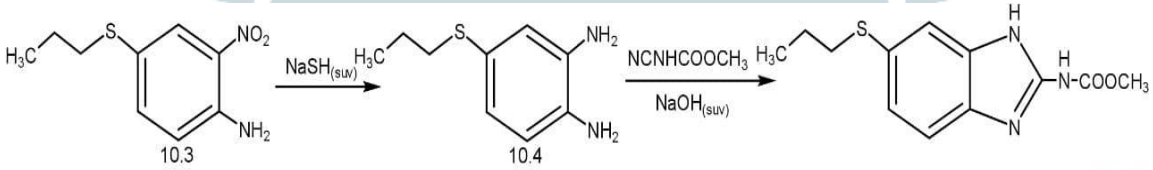


Due to the rotation of the methoxycarbonyl group relative to the N8-C9 amide bond in the albendazole molecule, we have two different conformational states, which are shown below.



In industry, albendazole is synthesized by reducing oxygen to produce 4-propylthio-o-phenylenediamine in aqueous media and this method is one of the most widely used methods.

This diamine is further reacted with the sodium salt of methyl N-cyanocorbamate to produce ABZ.



1-scheme

This synthesis method (Scheme 1) is a high yield, low cost process [7].

Recently, some forms of albendazole (Zentel, Helmadol, Nemozol, Sanoxal) have been very successfully used in the treatment of helminthiases due to their high therapeutic effect [8].

Albendazole is effective against tissue parasites, e.g.: Ascaris lumbricoides, Trichuris trichiura, Enterobius vermicularis, Ancylostoma duodenale, Necator americanus, Strongyloides stercoralis, including

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nematodes: askariyaz, trichocefaloz, ankilostomioz, enterobioz, nonkatoroz, toksokaroz, strongiloidiyoz, opistorxioz, giardiasis, mikrosporidioz and others used when treating symptoms.

The main mechanism of action of albendazole is associated with the selective stopping of the polymerization of β-tubulin, this leads to the destruction of cytoplasmic microtubules of the cells of the intestinal tract of helminths, suppresses the breakdown of glucose and stops the synthesis of ATP, blocks the movement of secretory granules and other organelles in the muscle cells of roundworms and kills them. When taken orally, albendazole is poorly absorbed from the gastrointestinal tract (less than 5%), in the liver it is converted into the main metabolite - albendazole sulfoxide II, which also has an anthelmintic effect. [9].

In addition, albendazole is metabolized to sulfoxide (II), albendazole sulfone (III) (secondary metabolite) and other oxidation products upon use. It should be noted that albendazole and its derivatives are poorly soluble in water, which interferes with their biological activity. Therefore, it is important to obtain their water-soluble forms and, i.e., to study their biological activity [10].

Based on the above, the purpose of the study is to obtain supramolecular complexes of albendazole with glycyrrhizic acid, with the monoammonium salt of glycyrrhizic acid and the monopotassium salt of glycyrrhizic acid in various ratios, as well as to determine their physicochemical constants and biological activity.

Result and Discussion: We have obtained supramolecular complexes of albendazole (ABZ) with glycyrrhizic acid (GA) and monopotassium salt of glycyrrhizic acid (MCSGA) in various ratios and determined some physicochemical constants. The results obtained are presented in Table 1.

Table 1

Physico-chemical parameters of supramolecular complexes of albendazole with GA and salts

Names of complexes	Complex ratio	Solubility of complexes in water (at 25°C)	Melting point C° (with expansion)
ABZ	-	insoluble	208-210
GA	-	slightly soluble	225-228
MCSGA	-	soluble	227-230
ABZ : GA	1 : 9	soluble	189-193
ABZ : GA	1 : 15	soluble	200-203
ABZ : GA	1 : 20	soluble	200-202
ABZ : MCSGA	1 : 9	soluble	215-218
ABZ : MCSGA	1 : 15	soluble	215-224

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ABZ : MCSGA	1 : 20	soluble	223-226

When analyzing the structure of the resulting complexes using IR spectroscopy, it was found that stretching vibrations of the -OH group of glycyrrhizic acid were observed at 3365-3363 cm-1. And in the IR spectrum of the ABZ:GA 1:9 supromolecular complexes, stretching vibrations belonging to the -OH group were detected in the form of broad shoulders in the regions of 3338–3325 cm-1. This shift and the appearance of a peak in the form of a broad shoulder indicates the formation of hydrogen bonds during complexation. It can also be observed that the frequency of vibrations belonging to the carbonyl group -C11=O in the carbon ring of the glycyrrhizic acid molecule shifts from 1656-1653 cm-1 to 1646-1644 cm-1. This shift is also confirmed by the large contribution of carbonyl groups to the formation of hydrogen bonds during complexation (Table 2).

Table 2

Results of spectroscopic analysis of the obtained supramolecular complexes of GA and its salts with albendazole

№	Names of complexes	Complex ratio	Fluctuations in the valence of OH groups (cm^{-1})	oscillation frequency, C_{11}=O (cm^{-1})	Stretching and bending vibrations of methyl and methylene groups. (cm^{-1})
1	GA		3363,86	1654,92	1122,57 1168,86 1192,01 1213,23
2	ABZ : GA	1 : 9	3332,99	1645,28	1166,93 1213,23 1255,66
3	ABZ : GA	1 : 15	3340,71	1645,28	1166,93 1211,30 1257,59 1327,03
4	ABZ : GA	1 : 20	3334,92	1645,28	1166,93 1213,23 1257,59
5	ABZ : MCSGA	1 : 9	3207,62	1653, 11	1172,72 1213,23 1261,45
6	ABZ : MCSGA	1 : 15	3209,55	1651,07	1170,79 1213,23 1261,45
7	ABZ : MCSGA	1 : 20	3230,77	1658,78	1260,02

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					1213,23 1261,45

However, a change in the frequencies of stretching and bending vibrations belonging to methyl and methylene groups also allows us to conclude that hydrophobic-hydrophobic interactions occur not only between hydrogen bonds, but also between non-polar parts of the molecule.

Further, high-performance liquid chromatography was used for qualitative and quantitative analysis of supramolecular complexes. During the analysis, the albendazole content in all obtained complex compounds was determined to be 97.0-99.9% of the theoretical amount.

The biological activity of the resulting supramolecular complexes, that is, anthelmintic properties, was tested in the laboratory using a method based on the ability of the drugs to have an anthelmintic effect on pharmaceutical leeches [11]. Experiments were carried out in 21 pieces of pharmaceutical leeches of average size in 7 groups of 3 animals for albendazole. Experiments show that leprosy paralysis and death were observed in albendazole at 190.00 seconds, in supramolecular complexes the earliest effect was observed in ABZ:GA 1:9 at 183.33 seconds, and the latest effect in ABZ: MCSGA 1:20 at 228 .00 seconds (Table 3).

Table 3

Results of studies of anthelmintic activity of supramolecular complexes.

№	Time of death (sec)	Average values
№ 1 ABZ : GA 1:9		
1	160	183,33 (168,19÷198,13)
2	185	
3	205	
№ 2 ABZ : GA 1:15		
1	190	206,00 (197,98÷218,68)
2	208	
3	220	
№3 ABZ : GA 1:20		
1	190	210,00 (128,19÷225,13)
2	210	
3	230	
№ 4 ABZ : MCSGA 1:9		
1	160	192,66 (172,19÷217,13)
2	198	
3	220	
№ 5 ABZ : MCSGA 1:15		

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1	178	211,00 (186,19÷235,13)
2	215	
3	240	
№ 6 ABZ : MCSGA 1:20		
1	197	228,00 (218,19÷256,13)
2	228	
3	259	
№ 7 ABZ		
1	180	190,00 (186,31÷193,68)
2	190	
3	200	

And so, supramolecular complexes were studied and positive results were obtained when testing small horned animals infected with helminthiasis ABZ-MCSGA 1:9, ABZ-GA 1:9, ABZ-GA 1:15.

CONCLUSIONS

We were the first to obtain water-soluble supramolecular complexes of albendazole with GA and MCSGA in various molar ratios.

The physicochemical constants of the resulting complexes were determined, their structure was studied and confirmed by UV and IR spectroscopy.

The anthelmintic properties of supramolecular complexes were determined in laboratory conditions with small horned animals and pharmaceutical leeches.

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