MECHANOCHEMICAL TECHNOLOGY FOR THE REGULATION OF THE SOLUBILITY OF ANTHELMINTIC DRUGS USING POLYMERS

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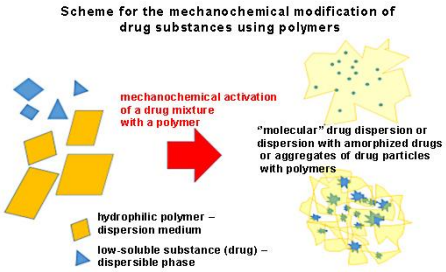
Abstract

Controlling the solubility of poorly water-soluble drugs remains one of the major challenges in the development of new effective drugs. The use of polymers is one of the promising routes for increasing the solubility of drug substances. This review summarizes the results of investigations on the application of oligosaccharides, polysaccharides, and other polymers to increase the solubility and bioavailability of anthelmintic drugs, which relate to different classes of organic compounds, by mechanochemical methods.



Key words: polymers, anthelmintics, solubility, mechanochemistry, efficacy.

Abbreviations

– albendazole (ALB)
– arabinogalactan (AG)
– cyclodextrin (CD)
– dioctyl sulfosuccinate (DSS)
– disodium salt of glycyrrhizic acid (Na_2GA)
– extract of licorice (EL)
– fenbendazole (FBZ)
– glycyrrhizic acid (GA)
– hydroxyethyl starch (HES)
– inclusion complex (IC)
– ivermectin (Iver)
– medamine (BMC)
– niclosamide (NA)
– polyvinylpyrrolidone (PVP)
– praziquantel (PZQ)
– simvastatin (SIM)
– sodium carboxymethyl cellulose (NaCMC)
– solid dispersion (SD)
– triclabendazole (TCB)

Introduction

One of the promising classes of organic compounds for the development of new antiparasitic drugs is comprised of benzimidazoles, which are mostly poorly soluble in water [1, 2]. Due to a solubility problem, many drugs have low bioavailability; therefore, improvement of the solubility of poorly soluble drug substances is an urgent task. One of the known methods for enhancing the solubility of such poorly soluble drugs is the use of water-soluble polymers [3]. Cyclodextrins (CDs) have been suggested as potential candidates owing to their ability to alter physical, chemical, and biological properties of drug molecules by forming inclusion complexes (ICs), which represent guest (drug molecule)–host (CD) systems. These complexes significantly change the properties of the guest drug molecule, including its solubility in water. Cyclodextrins have attracted great interest in pharmaceuticals since their ICs with hydrophobic drug molecules can penetrate body tissues and release drugs under certain conditions. CDs can be used for molecular encapsulation of many hydrophobic and/or unstable drugs. The encapsulated drugs can readily be wetted and are more soluble, which improves the bioavailability and modifies the properties of the drug [4]. In the pharmaceutical industry, CDs have been used as complexing agents to increase the aqueous solubility of poorly soluble drugs, their bioavailability and stability, as well as to improve drug delivery from almost any type of drug formulations [5]. For example, CDs can be used in the development of various drug delivery systems, such as liposomes, microspheres, microcapsules, nanoparticles, *etc.* [6, 7]. Solid dispersions (SDs) are one of the types of delivery vehicles that represent finely dispersed powders, ideally nanopowders, consisting of a hydrophilic matrix (water-soluble polymers/excipients) and a hydrophobic drug (possibly several drugs) [8].

Owing to the mentioned features, namely, the effect of CDs on the solubility of drugs, their bioavailability, safety, and stability, as well as their potential as drug delivery vehicles, studies on expanding the application scope of CDs and other polysaccharides for the creation of potentially active drugs are of particular importance. Dushkin *et al.* [9] explored the ability of *β*-cyclodextrin (*β*-CD) to complex with several drugs during their joint mechanical treatment at the drug/polymer mass ratio of 1:10. It was shown that an increase in the drug solubility under these conditions ranged within 1.8–15.1 times. In continuation of these studies, the mechanochemical complexation of drugs with other polysaccharides (arabinogalactan, hydroxyethyl starch, pectin, *etc.*) was explored

[10]. It was shown that the mechanochemical technology for increasing the solubility and effectiveness of drugs provides SDs that form stronger supramolecular complexes than complexes obtained by other alternative methods, in particular, by dissolution, melting, *etc*. Moreover, the innovative mechanochemical technology offers the following advantages over the other techniques:

– the possibility of obtaining target products in one technological stage;

– the absence of solvents and melts;

– the possibility of using original solid components (polymer, drugs) that do not have areas of joint solubility or decompose during melting/heating, as well as reacting with each other when they are dissolved;

– the flexibility of a technological process that allows for minimizing the occurrence of side undesirable chemical reactions.

The potential of the solid-phase mechanochemical modification in enhancing the parameters of solubility and pharmacological activity of the drugs was demonstrated by the examples of the drugs such as orthophenone, butadione, *etc.*, and polysaccharide glycyrrhizic acid (GA) [11]. The resulting SDs did not differ significantly from those obtained by the liquid-phase method in the ulcerogenic activity. The use of GA for the modification of the psychotropic drug azaleptin ensured the improvement of its solubility more than 20 times, which allowed for reducing the drug dosage and undesirable side effects. The features of the psychotropic action of the resulting complex were associated with the specific properties of GA itself, which is manifested in its interaction with receptors [12]. Complexes of poorly soluble simvastatin (SIM) with AG and a disodium salt of glycyrrhizic acid (Na_2GA) were obtained by mechanochemical technology to improve the solubility of SIM and increase its oral bioavailability [13]. *In vivo* pharmacokinetic tests in laboratory animals revealed a significant increase in the SIM bioavailability after administration in the form of a complex with Na_2GA or AG. Moreover, the inclusion complex of SIM and AG showed better results than SIM in reducing the total cholesterol levels. Based on the results of the use of polysaccharides to increase the solubility and effectiveness of poorly soluble drugs, many reports have been published, including reviews [6, 9, 14–20], which confirm the versatility of CDs and other polysaccharides as complexing agents for increasing the water solubility of poorly soluble drugs as well as their bioavailability and stability. In addition, they find application as drug delivery vehicles. Considering the ability of polysaccharides to act as delivery vehicles, the method of mechanochemical modification was used for the antihelminthic medamine (benzimidazole-2-carbamate (BMC)) in order to improve its solubility (8 mg/L) and bioavailability (Table 1). The use of polysaccharide, namely, apple pectin as a drug delivery vehicle afforded an increase in the solubility of the new drug medapec (BMC/pectin 1:9) to 45 mg/L [21]. At the same time, while maintaining the high activity against nematodes, medapec demonstrated also the high efficiency and good tolerance in the model of larval echinococcosis of white rats, which is the closest analog to the corresponding human pathology [22, 23]. This result was explained by the formation of the corresponding IC of medapec in water, which was confirmed by the data of IR spectroscopy and analysis of dissolution and penetration through a semi-permeable septum [21]. The proposed technology was extended to albendazole (ALB) and other polysaccharides (*β*-CD, HES, AG, *etc.*). The corresponding SDs of BMC and ALB with polysaccharides were obtained (Table 1) that represented nanodispersed powders (30–40% of nanoparticles with the sizes less than 0.1 mmc) with the enhanced solubility, for example, in 58 times for a solid dispersion of ALB/AG (1:9), which was recommended based on the results of *in vivo* testing for production trials of drugs in livestock complexes [24].

The goal of this review is to show the potential of mechanochemical technology in improving the solubility and effectiveness of anthelmintic drugs by the joint mechanical treatment of their substances with polysaccharides.

Methods for preparation of anthelmintic drugs and their properties

Using polymers to increase the solubility and effectiveness of benzimidazole anthelmintics

At the beginning of this section, it should be noted that drug SDs can be obtained by various methods [19], including dissolution methods. Thus, Castillo *et al*. [25] obtained a complex of ALB with *β*-cyclodextrin and an SD of the composition ALB/hydroxypropyl-*β*-cyclodextrin (1:1) that afforded a 40% increase in the bioavailability of ALB in comparison with its suspension form (Table 1). Continuing these studies, Kalaiselvan *et al.* [26] obtained an SD of the composition ALB/hydroxypropyl-*β*-cyclodextrin/L-tartaric acid (molar ratio 1:1:1) that was found to be absorbed even faster than the earlier known two-component SD, which was reflected in the improvement of the anthelmintic efficacy against *Trichinella spiralis*.

A solid dispersion of the composition ALB/PVP (1: 1) was obtained by dissolving the starting components in methanol followed by stirring for 24 hours after which the resulting solution was poured onto teflon sheets (Table 1). The solvent was evaporated in a partially open desiccator at room temperature for 3 days. The resulting films were carefully pulverized and dried at room temperature under vacuum [27].

Continuing investigations on the mechanochemical modification of anthelmintics using polymers (PVP, AG, GA and its derivatives), two benzimidazoles (ALB and fenbendazole (FBZ)) were explored [28]. The machining of the components was carried out in a metal drum with steel balls in a LE-101 roller mill (manufactured in Hungary). The resulting SDs were characterized by XRD, thermal analysis, SEM, IR spectroscopy, and dissolution in water. The IR spectroscopic studies revealed that the characteristic signals of the drug molecules are broadened due to the uniform distribution of their micronized particles over the polymer matrix. These data also confirmed that there are no chemical interactions involving the drug and polymer, but the corresponding intermolecular complexes may be formed owing to the forces, van der Waals interaction between the characteristic groups of the initial drug and polymer [29]. The test results confirmed a broad spectrum of anthelmintic activity of the obtained complexes against nematodes of sheep with the dose of ALB and FBZ reduced

almost 10 times. When animals tolerated drugs well, their side effects on the body were not observed (Table 1).

The mechanical treatment of ALB with AG provided a solid dispersion of the ALB/AG composition (1:9) that was studied by different physicochemical methods both in the solid state and in an aqueous solution [30]. According to the electron microscopy data, ALB is a partially amorphous powder with an average particle size of 20–30 microns, while AG consists of spherical particles with an average size of 5–20 microns. During mechanochemical processing, the ALB and AG particles undergo destruction followed by the formation of a polydisperse powder that consists mainly of the particles of irregular shapes (with the size of 5–20 μm) and their aggregates. According to the XRD analysis, the resulting dispersion lacks a crystalline phase of ALB (Table 1). The formation of an inclusion complex was confirmed by the method of intrinsic solubility and NMR relaxation. It was shown that the SDs synthesized mechanochemically are more stable than the complex obtained by mixing solutions of the components. The investigation of their anthelmintic activities against *Trichinella spiralis*, *Hymenolepis nana*, *Fasciola hepatica*, and mixed nematodes of sheep confirmed the high efficiency at the 10 times lower doses compared to that of free ALB and revealed the reduced acute toxicity and hepatotoxicity. These results indicate that the SDs and complexes based on ALB with AG are potential candidates of therapeutic agents for veterinary medicine [31]. Similarly, AG was used for the modification of FBZ: the resulting solid dispersion of the composition FBZ/AG (1:9) exhibited enhanced solubility (18 times) and 100% efficiency in dictyocaulosis, strongyloidosis, and strongylatoses of the digestive tract and 98.3% activity in sheep trichocephalosis at the FBZ dose of 3.0 mg/kg, whereas the recommended dose of the standard drug is 5.0 mg/kg [32, 33].

The modification of FBZ with PVP afforded a solid dispersion of the FBZ/PVP composition (1:9), which was analyzed by different physicochemical methods. The latter confirmed an increase in the solubility, a reduction in the sizes of the FBZ and polymer particles, the amorphization of FBZ, and its inclusion in the composition of PVP micelles (Table 1) [34]. The results of the XRD analysis indicated the loss of FBZ crystallinity and the presence of an amorphous state in the case of the SD due to the plasticity of PVP, which facilitates mixing of the components at the molecular level and enables the appearance of an "X-ray amorphous" state [35] that increases the SD dissolution in 2.8 times. The micrographs showed that PVP consists of spherical particles with the average sizes of 10–100 μm, whereas FBZ consists of particles with the average sizes of 5–30 μm. After the mechanical treatment, FBZ particles and spherical PVP particles were destroyed affording polydisperse powder that consisted of their aggregates with the average sizes of 5–20 μm. Thus, the substance and polymer were crushed to irregularly shaped aggregates, which favors the interaction of FBZ with PVP. The effectiveness of the resulting SD was studied in a laboratory model of infection with *Hymenolepis nana* and *Trichinella spiralis* in mice and helminthiasis in sheep. It was found that the SD is more active than the main substance of FBZ, and its anthelmintic properties are better. The results obtained substantiate the possibility of creating innovative drugs for the treatment of helminthiasis at the reduced doses.

The addition of an emulsifier, namely, a sodium salt of dioctyl sulfosuccinate (DSS), to the fenbendazole/PVP system ensured the formation of an SD upon their joint mechanical treatment that features 24 times higher solubility (Table 1) and exhibits 100% efficiency in trichinosis and hymenolepiasis of white mice and gastrointestinal strongilatosis and monieziosis of sheep at the FBZ doses of 2.0 and 3.0 mg/kg, which are lower than the recommended doses of the standard drug [36, 37].

The extract of licorice (EL) containing at least 25% of GA in its composition displays a broad spectrum of biological activity, serves as a promising component for the innovative drugs [38], and forms micellar structures with the inclusion of drugs in its composition [39], which can be considered as potential drug delivery systems. Taking into account these peculiarities of EL, its complexation with ALB upon joint mechanical treatment at different ratios of the components was studied (Table 1) [40]. At the mass ratio ALB/EL = 1/20, a solid dispersion was obtained in the form of a light brown powder (SD-1). Similarly, SDs with the ALB/EL ratios of 1:10 (SD-2), 1:9 (SD-3), and 1:4 (SD-4) were prepared. Their solubilities significantly differed from that of the original ALB. Thus, SD-1 demonstrated a 17-fold increase in the solubility after three hours of the mechanical co-treatment of ALB with EL, whereas, on passing to SD-2, SD-3, and SD-4, the solubility decreased up to 13 times as the ALB content increased from 9% to 20%. The greatest increase in the solubility was observed in the case of the drug in the form of a suspension. In the physical ALB/EL (1:20) mixture, the solubility of ALB increases only 3 times. In the experiments on sheep naturally infected with nematodirus and other types of strongylates of the digestive tract and moniesia, it was shown that, at the dose of 2.0 mg/kg of ALB, all the SDs obtained show 90.1–91.7% effectiveness against *Nematodirus* spp., 89.5–92.4% effectiveness against other types of gastrointestinal strongylates, and 98.6–100% effectiveness against *Moniezia expansa*, which is 4–5 times higher than the activity of ALB.

Expanding the possibilities of EL for modifying the properties of other benzimidazole preparations, the joint mechanical treatment of FBZ with EL was carried out in the presence of the emulsifier DSS with the mass ratio of the components 1:8.9:0.1 [41]. The formation of a solid dispersion was confirmed by an increase in the solubility up to 27 times, while the solubility of a physical mixture increased only 2.6 times (Table 1). Analyzing the IR spectra, it was found that the process of joint machining of FBZ with EL does not lead to mechanical destruction of FBZ. Based on the displacement of the characteristic bands of the initial FBZ, an assumption was made about the formation of an intermolecular complex of FBZ with EL (a shift of the main characteristic bands of GA). The comparison of diffraction patterns of the initial FBZ and its SD indicated that, upon mechanical treatment for 2 h, the crystallinity of the initial FBZ does not change, despite a decrease in the intensity of reflections. It was concluded only about the micronization of the FBZ sample with the preservation of the initial crystallinity. However, the addition of an amorphous-crystalline sample of the polymer (EL) to crystalline FBZ and joint machining afforded a reduction in the crystallinity of FBZ to 20%. The results of the XRD analysis show that the degree of amorphization of fenbendazole in a solid dispersion of the composition FBZ/EL (1 : 9) reaches an optimal value (10%) already during processing for 150 min, while further treatment

(up to 420 min) does not reduce significantly the crystallinity of FBZ. Based on the results obtained, it was confirmed that an increase in the anthelmintic effect is associated with a decrease in the size of the FBZ particles, loss of crystallinity, amorphization and inclusion of its molecules on the surface and inside the pores of LE and, as a consequence, an increase in the solubility and permeability through biological membranes.

To extend the technology of mechanochemical modification to triclabendazole (TCB), ten water-soluble polymers and excipients were used (HES, PVP, AG, NaCMC, *etc.*) [42]. The resulting SDs were finely dispersed, free-flowing, water-soluble powders with particle sizes up to 1–10 microns (Table 1). In these cases, an increase in the solubility ranged from 3 to 25 times, depending on the nature of the polymer. The highest solubility was observed for the SD of the composition TCB/AG (1:9) which was called Triclafascid. AG included in this drug is widely used in medicine and veterinary medicine [43] and thus was used in this innovative drug Triclafascid. Since fascioles, localized in the bile ducts, cause their thickening, fatty degeneration, and cirrhosis of the liver, AG, which possesses noticeable hepatoprotective and membranotropic properties, provides high bioavailability of Triclafascid to parasites [44].

The mechanochemical technology for obtaining SDs was also effective with the mixtures of anthelmintic substances. The practice of using mixed preparations is an objective necessity because of a wide range of helminths. Therefore, upon simultaneous invasion of the digestive tract of sheep with fascioles and nematodes, the use of SD based on ALB and TCB with PVP enables 100% efficiency with a single oral administration at the dose of 4.0 mg/kg. This dose is 5 times lower than the previously known therapeutic dose of the components. A mixture of ALB and TCB substances in the same dose showed weak efficacy: 22.0 and 24.5%, respectively [45]. This can be explained by the fact that the SD of the composition ALB/TCB/PVP (1:1:8) features the increased solubility of the components (ALB in 14 times; TCB in 8 times). In addition, an advantage of this SD is that it contains ALB, which has no embryotropic effect. Taking into account the peculiarity of parasite infestation of animals in the Altai Republic, parasitologists proposed to develop solid dispersions based on three anthelmintics (FBZ, TCB, and ivermectin (Iver)). PVP was chosen as a polymer. The SDs of the following compositions were obtained by mechanochemical technology: FBZ/PVP (1:9), TCB/PVP (1:9), FBZ/Iver/PVP (1:1: 9), and TCB/Iver/PVP (1:1:9). They displayed the increased solubility (from 14 to 29 times) [46, 47]. The investigation of antiparasitic activity in 140 sheep showed the high efficiency of the SD at the FBZ dose of 3.0 and that of Iver of 0.2 mg/kg on the following parasites: *Strongylata*, *Moniezia expansa*, and *Melophagus ovinus*, while the therapeutic doses of FBZ and Iver are 5.0 and 1.0 mg/kg, respectively. The SD based on TCB showed high efficacy against gastrointestinal *Strongylata* and *D. Dendriticum* and was not effective against *Moniezia expansa*. The initial substances, FBZ and TCB, showed significantly lower efficacy for helminthiasis in sheep. The high parasiticidal activity of the compositions explored was explained by the increased solubility in water and bioavailability. A three-fold decrease in the dosage of FBZ and TCB in the SD did not lead to a decrease in their anthelmintic activity. Similarly, the SDs of the Iver/AG (1:10) and ALB/Iver/AG (1:1:10) compositions were obtained that exhibited the enhanced solubility (up to 12 and 33 times, respectively) (Table 1). The study of the antiparasitic activity of these SDs against intestinal strongylitis, moniesiasis and melophagosis of sheep (70 pcs) showed that their efficiency at the Iver dose of 0.2 mg/kg and that of ALB of 2.0 mg/kg (which is 5 times lower than the corresponding therapeutic doses of the standard drugs used in practice) reached 91.4–100%. At the same time, the initial substances at the same dosages were found to be less effective [48].

An important feature of the drugs obtained by the mechanochemical modification of anthelmintic substances using polymers is the possibility to create new drugs with an extended spectrum of biological activity. This was earlier detected [21–23] for the drug medapec, which, retaining the high activity against nematodes, showed also the high efficiency against larval echinococcosis of white rats. Similarly, upon modification of ALB with AG, the resulting solid dispersions of the ALB/AG compositions of 1:10 and 1:20 (mass ratios) formed upon dissolution in water the ICs featuring the solubility enhanced up to 40 times, which is not characteristic of ALB (Table 1) [49]. They exhibited the high anthelmintic activity in the *Opisthorchis felineus* model of opisthorchiasis, which exceeded the activity of official drugs, including praziquantel [50]. These results suggest the possibility of creating anti-opisthorchiasis drugs based on the substances that do not exhibit such an effect on their own.

For the well-known anthelmintic praziquantel (PZQ), a combination of mechanochemical activation and spray congealing technology has been proposed for the treatment of schistosomal infections in children [51]. The mechanical activation of PZQ with PVP at the 1:1 mass ratio in a vibration mill under cryogenic conditions afforded a polymer that was loaded into microparticles using a spray congealing technology (Table 2). The analysis of physicochemical properties of the resulting SD revealed the improvement of particle morphology, wettability, and solubility, as well as an increase in the biopharmaceutical properties.

The versatility of mechanochemical technology for the modification of poorly soluble drugs was confirmed by its expansion to the anthelmintics based on other classes of organic compounds (for example, the isoquinoline derivative praziquantel and the salicylanilide derivative niclosamide).

The mechanochemical modification of PZQ with Na_2GA afforded a solid dispersion which, upon dissolution in water, led to the incorporation of praziquantel molecules into micelles formed in a solution of Na_2GA [52]. Investigations on the opisthorchiasis model *Opisthorchis felineus* revealed a significant increase in the anthelmintic activity of PZQ (4–11 times) compared to that of the initial PZQ, whereas the use of the composition PZQ/Na_2GA (1:10) improved the bioavailability of PZQ in 3 times. In continuation of these studies, this composition was further explored for other physicochemical and anthelmintic properties [53]. The scanning electron micrographs showed that the original PZQ consists of crystalline elongated particles 10–20 μm in size and their aggregates up to 500 μm in size. The original Na_2GA consists of spherical particles with sizes of 5–50 μm. The solid dispersion obtained after joint machining consisted of the particles with the average sizes of 5–20 microns and their aggregates. In this case, PZQ appeared to be distributed in an excess of the amorphous Na_2GA matrix, forming a guest–host system (Table 2).

Table 1. Use of polymers for creating benzimidazole anthelmintics

Active substance	Composition of the anthelmintic drugs	Method for obtaining	Properties of new drugs	Ref.
Medamine (BMC)	BMC/pectin (1:9)	Mechanochemical modification in an AGO-2 planetary centrifugal mill	I. Increased solubility of BMC (9 times) and high efficacy against nematodes at the low BMC concentration II. New type of activity—high efficiency against larval echinococcosis of white rats	[21–23]
BMC, Albendazole (ALB)	AG, HES, β-CD	Mechanochemical modification in a LE-101 roll ball mill	I. Increased solubilities of SDs (3–58 times) II. Potential drugs against echinococcosis	[24]
ALB	I. ALB/hydroxypropyl β-CD (1:1) II. ALB/hydroxypropyl β-CD/l-tartaric acid (1:1:1)	Freeze drying	Increased bioavailability and efficacy against encapsulated *Trichinella* larvae	[25, 26]
ALB	ALB/PVP (1:1)	Dissolution method	Increased bioavailability and larvicidal activity	[27]
ALB, Fenbendazole (FBZ)	AG, HES, PVP	Mechanochemical modification in a LE-101 roll ball mill	Enhanced water solubility and anthelmintic activity in experiments against nematodes of the gastrointestinal tract at 9–10 times lower substance doses	[28, 29]
ALB	ALB/AG (1:9)	Mechanochemical modification in a LE-101 roll ball mill	Increased solubility and anthelmintic activity against *Trichinella spiralis*, *Hymenolepis nana*, *Fasciola hepatica*, and mixed nematodes of sheep	[30, 31]
FBZ	FBZ/AG (1:9)	Mechanochemical modification in a LE-101 roll ball mill	Increased solubility of FBZ, reduced particle sizes, amorphization of FBZ, and high efficacy against *Hymenolepis nana* and *Trichinella spiralis* infection of mice and helminthosis of sheep at the reduced doses	[32, 33]
ALB	ALB/EL (1:4) ALB/EL (1:9) ALB/EL (1:10) ALB/EL (1:20)	Mechanochemical modification in a LE-101 roll ball mill	Increased solubility (up to 13 times) and high efficacy against *Nematodirus spp*., other types of gastrointestinal strongylates, and *M. expansa* at the doses 4–5 times lower than that for the initial ALB	[40]
FBZ	FBZ/EL/DSS (1:8.9:0.1) Dioctyl sulfosuccinate (DSS)	Mechanochemical modification in a LE-101 roll ball mill	Increased anthelminthic activity owing to the smaller FBZ particle sizes, loss of crystallinity, amorphization, and inclusion of its molecules on the surface and inside the pores of polymers; increased solubility and permeability through biological membranes	[41]
Triclabendazole (TCB)	TCB/AG (1:9) TCB/PVP (1:9) TCB/Pectin (1:9) TCB/NaCMC (1:2) TCB/HES (1:9)	Mechanochemical modification in a LE-101 roll ball mill	Increased solubility of SDs (3–25 times); efficacy SDs against Fascioliasis 4–5 times higher than that of the initial TCB	[42–44]
ALB and TCB	ALB/TCB/PVP (1:1:8)	Mechanochemical modification in a LE-101 roll ball mill	Increased solubility of ALB (14 times) and TCB (8 times) for the SD which does not display any embryotropic effect of ALB; high efficacy against fasciols and nematodes at the doses 5 times lower than that of the standard drugs	[45]
FBZ, TCB, and ivermectin (IVM)	FBZ/PVP (1:9) TCB/PVP (1:/9) FBZ/IVM/PVP (1:1:9) TCB/IVM/PVP (1:1:9)	Mechanochemical modification in a LE-101 roll ball mill	Increased solubility of AS (14–29 times) and high efficacy against parasites Strongylata, *Moniesia expansa*, and *Melophagus ovinus* at a 3-fold reduction in the dosages of FBZ and TCB	[46–48]
ALB	ALB/AG (1:10) ALB/AG (1:20)	Mechanochemical modification in a VM-I roll ball mill	Increased solubility of the SDs and their high anthelmintic activity in the model of *Opisthorchis felineus*, which exceeded the activity of the official drugs, including that of praziquantel; new type of biological activity for ALB	[49, 50]

The results on measuring the transmembrane drug transfer showed that the diffusion rate of PZQ molecules from its composition with Na_2GA is significantly higher than that for the initial substance. An almost 2-fold acceleration of the transmembrane transfer from the complex solution was achieved. Therefore, the authors suggested that Na_2GA serves as a carrier for the PZQ molecules due to the *in situ* formation of micelles upon dissolution of the drug composition [54]. This conclusion was further supported while studying the interaction of GA with lipid models [55]: a change in lipid mobility was associated with the integration of GA molecules into the lipid bilayer, which can affect the permeability of a cell membrane. The biological studies of the proposed composition PZQ/Na_2GA (1:10) showed its high efficiency on hamsters infected with *Opisthorchis felineus* and the improved physiological state [56].

Niclosamide (NA) is the anthelmintic agent that is widely used to treat cestode infections in animals. The solid-phase mechanical treatment of NA with PVP was carried out in one step in a LE-101 ball mill with the controlled energy intensity (process module, drum rotation speed, *etc.*) [57]. The resulting solid dispersion of the composition NA/PVP (1:9) (Table 2) consisted of the particles and their aggregates ranging in sizes from 0.1 to 10 μm, which were characterized by the following parameters:

– it was found that a decrease in the intensity of the NA crystallinity, accompanied by the disappearance of its reflections in the XRD pattern because of disordering of its crystal structure, facilitates the formation of solid dispersions with polymers in the amorphous state. The resulting SDs afford the corresponding supramolecular complexes upon dissolution in water.

– photomicrographs showed that PVP powder is composed of 0.1–0.5 mm particles, while NA powder features a wider range of particle sizes (50–250 μm). During mechanochemical processing, the crystalline NA particles and spherical PVP particles were destroyed and the aggregates of irregular shape were formed.

These results confirmed the formation of intermolecular complexes of NA due to hydrogen bonding between their functional groups and the polymer, van der Waals and hydrophobic interactions, adhesions, *etc*. As a rule, NA is evenly distributed in the pores and on the surface of PVP as a carrier. This distribution significantly changes the properties of the drug and provides targeted delivery of the drug owing to the release of the active substance and its transport through the biological membrane to the action site. The study of the solubility of the starting substance NA in water showed that there is a noticeable change in this indicator, namely, the solubility of the 1:5; 1:10, and 1:20 compositions increased in 11.0, 19.0, and 26.7 times, respectively. The investigation of the anthelmintic efficacy of the resulting SDs demonstrated their high efficacy in various ratios (1:10; 1: 5, and 1:20) at the dose of 20 mg/kg of NA when administered orally against *Hymenolepis nan*a in mice and *Moniezia expansa* in sheep, whereas NA was not effective at the same dose [58].

The mechanochemical modification of niclosamide with AG and silica (SiO_2) afforded SDs of various compositions with the increased solubility in water, which also demonstrated the improved anthelmintic activity. Indeed, in cattle moniesiasis, the solid dispersions NA/PVP (1:2) and NA/AG (1:5) at the dose of 20 mg/kg provided 100% efficiency (Table 2), whereas the efficiency of the solid dispersion NA/SiO_2 (1: 2) was 73–75%. At the same time, the required dose of the solid dispersion (20 mg/kg) was 5 times lower than that of the basic drug NA (100 mg/kg) [59]. The SD of the composition NA/AG (1:2) showed 100% efficiency for anoplocephalidosis of horses at the dose of 20 mg/kg, while the SDs of the compositions NA/PVP (1:2), NA/SiO_2 (1:2), and NA/AG (1:5) demonstrated only 75–87% efficiencies [60].

Based on the results presented, it can be concluded that polymers not only contribute to an increase in the solubility of poorly soluble anthelmintic substances but also serve as promising carriers for the targeted delivery of anthelmintic drugs. Some of them, for example, GA and its sodium salt are capable of forming self-associates. In these cases, the poorly soluble drug molecules appear to be included in the structures of micelles; which affords an increase in their concentration in solution and transmembrane transfer.

Table 2. Use of polymers for creating miscellaneous anthelmintics

Active substance	Composition of anthelmintic drugs	Method for obtaining	Properties of new drugs	Ref.
Praziquantel (PZQ)	PZQ/PVP (1:1)	Combination of the mechanochemical activation and spray congealing technology	Increased biopharmaceutical efficacy against *Schistosoma mansoni*	[51]
PZQ	PZQ/Na_2GA (1:10)	Mechanochemical modification in a VM-I roll ball mill	Increased solubility, reduction of particle sizes, amorphization of the substance, and high anthelmintic efficacy at the reduced doses	[52–54]
Niclosamide (NS)	NS/PVP (1:5) NS/PVP (1:10) NS/PVP (1:20)	Mechanochemical modification in a LE-101 roll ball mill	Increased solubility of the SDs with 1:5, 1:10, and 1:20 ratios of the components (11.0, 19.0, and 26.7 times, respectively); high efficacy at the dose of 20 mg/kg against *H. nana* in mice and *M. expansa* in sheep (NS was not effective at the same dose)	[57, 58]
NS	NS/AG (1:5) NS/PVP (1:2) NS/SiO_2 (1:2)	Mechanochemical modification in a LE-101 roll ball mill	Increased solubility and 100% anthelmintic activity of the resulting SD (NS/AG) against anoplocephalidosis of horses	[59, 60]

Conclusions

A brief review of the reports devoted to the application of water-soluble polymers for improving the solubility of poorly soluble substances of anthelmintic drugs during their joint mechanical processing shows the great potential of this approach for obtaining innovative drugs that can be used in the field of animal health protection. This technology is versatile and has been successfully applied to the development of drugs for medicine and agriculture [61–63]. The advantages of the proposed solid-phase mechanochemical technology for creating new drugs with the increased solubility and bioavailability are as follows:

– this approach can be realized as a one-stage process since the preparation is accomplished in a single step when the initial components are loaded into the drum of a ball mill;

– the mechanochemical technology enables the production of drugs not only from two components but also from more components without restrictions due to the impossibility of selection of the solvents with common areas of dissolution;

– the method is versatile because it is acceptable for a wide range of biologically active substances used in medicine and veterinary;

– it obviates the need for using organic solvents, which are explosive and flammable and can lead to the formation of a large amount of waste;

– the mechanochemical process is scalable.

The results presented show great opportunities for the so-called green mechanochemical technology as a low energy-consuming, solvent-free, and ecologically friendly technique for the production of drugs of a broad range of activity with high efficiency while reducing the norm/dose of their use.

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