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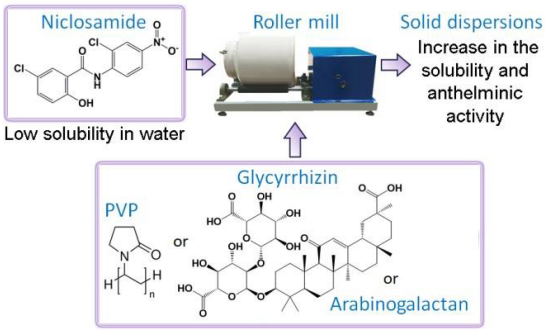
NICLOSAMIDE SUBSTANCE: MODIFICATION, ANALYSIS, AND BIOLOGICAL ACTIVITY

S. S. Khalikov,*[a] I. A. Godovikov,[a] B. V. Lokshin,[a] A. M. Pak,[a] E. A. Khakina,[a,b] M. M. Babaskina,[a,b] M. M. Ilyin,[a] and L. V. Anikina[c]

[a] *Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, str. 1, Moscow, 119334 Russia*
[b] *National Research University Higher School of Economics, ul. Vavilova 7, Moscow, 101000 Russia*
[c] *Institute of Physiologically Active Substances, Russian Academy of Sciences, Severnyi proezd 1, Chernogolovka, Moscow Oblast, 142432 Russia*

Abstract

The niclosamide substance (NCS) is a part of many anthelmintic and anticancer drugs. However, it has a serious drawback—the low solubility in water and physiologically active media, which leads to the high dosage required to achieve a therapeutic effect, increased cost, and enhanced toxicity. To improve the solubility of NCS, its mechanochemical modification with polymers has been suggested. This allows for increasing the solubility of NCS in 40–52 times. Such an increase in this parameter is shown not to affect the cytotoxic activity adequately. The observed selectivity towards different cancer cell cultures is discussed.



Key words: niclosamide, solid dispersion, chemical stability analysis, solubility, infrared spectroscopy, ^{1}H nuclear magnetic resonance spectroscopy, scanning electron microscopy, biological activity.

Introduction

The solubility of drug substances is an important characteristic that determines not only the prospects for a future pharmaceutical, but also the choice of its dosage form to change bioavailability and enhance efficiency. One of the methods for increasing the solubility of such substances is the production of their solid dispersions (SD) with hydrophilic polymers [1].

The well-known anthelmintic niclosamide, which has high cestocidal and trematocidal activity, is included in the World Health Organization list of essential medicines for children [2]. Recently, we have demonstrated that a SD obtained by combined solid-phase treatment of the niclosamide substance (NCS) and polyvinylpyrrolidone (PVP) holds great promise for veterinary applications [3].

Along with the fact that NCS is used to treat people infected with tapeworms, it has also been shown to serve as a promising basis for anticancer drugs [4]. However, the low solubility of NCS prevents its widespread use. Therefore, the development of dosage forms that could increase its solubility, bioavailability, and efficiency is quite urgent. For this purpose, the following methods are used:

– micronization of the substance particles in an aqueous medium [5] and emulsification with copolymers [6];

– production of nanosuspensions [7, 8] and solid lipid nanoparticles [9];

– production of SDs, in particular, by mechanochemical modification of NCS [10].

Among the most promising polymeric compounds used for obtaining effective drug SDs, of particular interest are glycyrrhizic acid (GA) and its disodium salt, which significantly improve the solubility of NCS (in 40–50 or more times) and act as versatile delivery systems due to their amphiphilic and membranotropic properties [11]. Owing to the latter, GA is able to form micelles in aqueous solutions and host–guest complexes with various hydrophobic molecules [12, 13]. The disodium salt of GA (Na_2GA) forms solutions with the lower viscosity; therefore, a synergistic effect can be expected when using this salt as a drug delivery system. This was confirmed by Meteleva *et al.* [14, 15] using the composition obtained by the combined mechanical processing of praziquantel and Na_2GA, which showed enhanced permeability and bioavailability in experiments on laboratory mice.

It was established that GA is able to interact with the cell membrane, affecting its properties such as elasticity and permeability [16], penetrating into the phospholipid bilayer and forming self-associates inside it, which lead to a change in lipid mobility and an increase in the permeability of cell membranes relative to drugs.

Taking into account the advantages of GA in the development of drugs, it seemed interesting to obtain the SDs based on niclosamide with GA and its derivatives in order to study their physicochemical properties and bioactivity.

Results and discussion

Changes in the solubility of niclosamide compositions with polysaccharides

To expand the range of polymers used for the modification

of NCS, the following polysaccharides were chosen: arabinogalactan (AG), glycyrrhizic acid (GA), and its disodium salt (Na_2GA) at a mass ratio of 1:9. The resulting SDs and the data on the solubility changes are presented in Table 1.

Table 1. Solubility of niclosamide and its solid dispersions with the polymers

Sample composition and production conditions	Solubility, mg/L	
	absolute	augmentation
Initial niclosamide (without mechanical treatment)	5.0	–
Mechanical mixture of the NCS/PVP (1:9) composition (grinding in a mortar)	8.5	1.7
SD of the NCS/PVP (1:9) composition after 2 h of mechanical treatment (MT) in an LE-101 roller mill	45.5	9.1
SD of the NCS/PVP (1:9) composition after 4 h of MT	78.5	15.7
SD of the NCS/PVP (1:9) composition after 6 h of MT	92.5	18.5
SD of the NCS/PVP (1:9) composition after 7 h of MT	93.0	18.6
Mechanical mixture of the NCS/AG (1:9) composition (grinding in a mortar)	7.7	1.5
SD of the NCS/AG (1:9) composition after 2 h of MT	36.3	7.3
SD of the NCS/AG (1:9) composition after 4 h of MT	66.9	13.2
SD of the NCS/AG (1:9) composition after 6 h of MT	89.2	17.8
SD of the NCS/AG (1:9) composition after 7 h of MT	89.5	17.9
Mechanical mixture of the NCS/GA (1:9) composition (grinding in a mortar)	10.1	2.0
SD of the NCS/GA (1:9) composition after 2 h of MT	41.8	8.4
SD of the NCS/GA (1:9) composition after 4 h of MT	90.5	18.1
SD of the NCS/GA (1:9) composition after 6 h of MT	203.5	40.7
SD of the NCS/GA (1:9) composition after 7 h of MT	207.5	41.5
Mechanical mixture of the NCS/Na_2GA (1:9) composition (grinding in a mortar)	16.5	3.3
SD of the NCS/Na_2GA (1:9) composition after 2 h of MT	63.3	12.7
SD of the NCS/Na_2GA (1:9) composition after 4 h of MT	142.2	28.4
SD of the NCS/Na_2GA (1:9) composition after 6 h of MT	255.0	51.0
SD of the NCS/Na_2GA (1:9) composition after 7 h of MT	259.0	51.8

The analysis of the results obtained show that an increase in the solubility of NCS depends on both the nature of the polymer and the processing time. Specifically, the maximum increase in the solubility (up to 42–52 times) is achieved in the case of GA and its disodium salt, presumably due to their remarkable amphiphilic properties and the formation of supramolecular complexes, as was noted earlier [12–15].

Chemical stability of niclosamide in the solid dispersions

To confirm the chemical stability of NCS during its mechanical treatment with the polymers, the compositions were analyzed by HPLC (Fig. 1), LC–MS (Fig. 2), and IR spectroscopy (Fig. S1 in the Electronic supplementary information (ESI)).

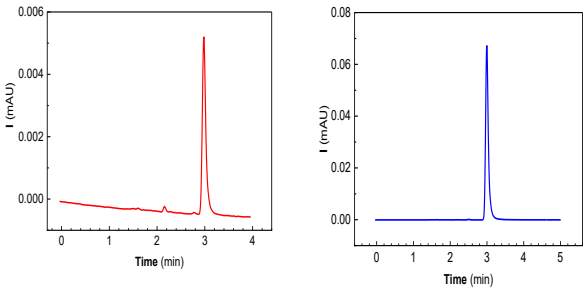


Figure 1. Chromatograms of the water solubility of initial niclosamide (**A**) (336.8 nm) and the SD of the NCS/PVP (1:9) composition after mechanical treatment for 7 h (**B**).

As can be seen from Figs. 1A and 1B, there are no additional peaks on the chromatogram of the sample subjected to mechanical treatment for 7 h. Moreover, the analysis of all the SDs after processing for the NCS intactness, namely, the chemical stability of NCS confirmed its calculated content (9.95 + 0.05%).

The results of the LC–MS analysis performed for the samples of neat NCS and its composition with PVP are presented in Figs. 2A and 2B. Figure 2A shows that the peak with a retention time of 3.45 min corresponds to NCS. The signals with m/z 325.1 and 653.2 correspond to $[M–H]^-$ and $[2M–H]^-$ ions, respectively.

Figure 2B shows the data for the NCS/PVP (1:9) composition after 3 h of mechanical treatment. The chromatogram shows only the peak of neat NCS. There were not observed any products of NCS decomposition, which was also supported by the quantitative determination of NCS using the external standard method. The sample contained 0.1% of NCS, which corresponds to the drug loading used to obtain the SD.

The lack of chemical degradation of NCS was also confirmed by the results of LC–MS analysis performed for the SDs of the NCS/Na_2GA (1:9) and NCS/AG (1:9) compositions after 7 h of mechanical treatment.

It should be noted that an additional component with m/z 293.2 (negative ions) was detected while studying the SD sample of the NCS/GA (1:9) composition. The quantitative determination of NCS in this SD led to a result that coincided with that calculated from the expected SD composition. Therefore, the additional component is not a product of NCS degradation. Presumably, it results from the destruction of GA.

The IR spectra of niclosamide, initial polysaccharides (GA and Na_2GA), and their SDs obtained after 6 h of mechanical treatment are depicted in Figs. 1SA and 1SB in the ESI, which show the superposition of the bands of two components. Noteworthy, there are no new clearly expressed absorption bands. The lack of the latter implies that mechanical treatment does not lead to chemical transformations of the components and the formation of new chemical compounds, which is in good agreement with the above-mentioned results of chromatographic analysis. However, it should be noted that some absorption bands of NCS appeared to be shifted in the SD spectra compared to the spectrum of the initial substance. This may be associated

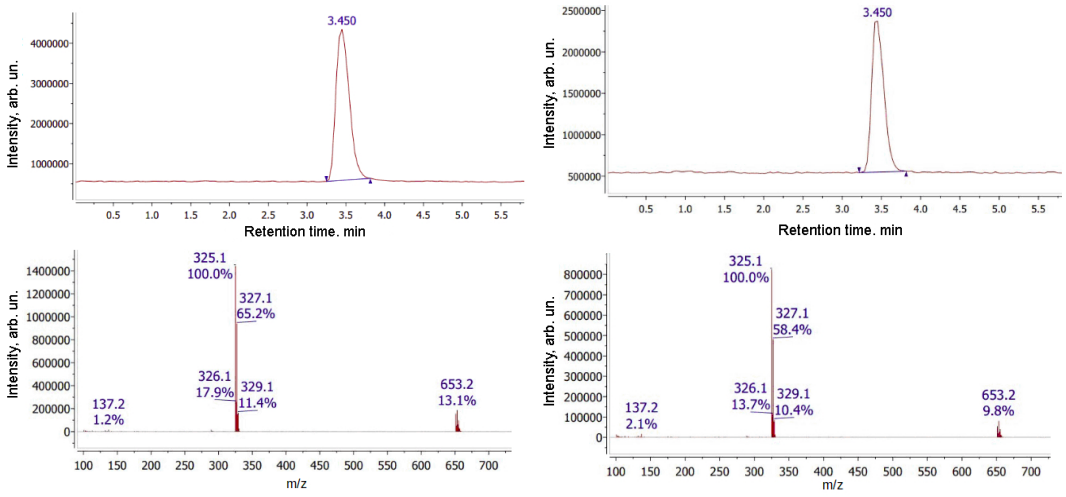


Figure 2. Total ion current chromatograms for negative ions obtained for the NCS standard (**A**, top) and the SD of the NCS/PVP composition after 3 h of mechanical treatment (**B**, top) and the mass spectra corresponding to 3.45 min (bottom).

with a change in the system of intermolecular bonds during mechanical treatment (for example, the formation of hydrogen bonds between NCS and a polysaccharide), which is likely to cause an increase in the solubility of the corresponding SD.

To confirm the changes in the properties of NCS after its mechanochemical modification with polysaccharides, the resulting compositions were analyzed by NMR spectroscopy and scanning electron microscopy (SEM).

Glushenko *et al.* [17] used the NMR spectroscopic data to substantiate the formation of supramolecular complexes in solutions by analyzing relaxation times T_2. The analysis of the ^{1}H NMR spectra and the resulting relaxation times of protons using the example of the NCS system and its SD with GA (Fig. S2A in the ESI) revealed an upfield shift of the NCS aromatic protons in the SD sample of the NCS/GA (1:9) composition (*i.e.*, the values of their chemical shifts decreased), while the relaxation times of protons (T_2) in most positions of NCS reduced in this case. These data appear to indicate the formation of aggregates involving the mentioned structural fragments, which is in good agreement with the previously reported data [17]. Similar relationships were observed when comparing the systems NCS/SD with Na_2GA and NCS/SD with AG.

The analysis of the NCS sample and its SD with PVP (Fig. S2B in the ESI) showed that most of the NCS signals were slightly downfield shifted, while the relaxation times of almost all the NCS groups also slightly decreased. The only exceptions were the two signals with δ = 8.76 and 7.04 ppm, which were characterized by a slight increase in the relaxation times from 1.13 to 1.17 s and from 0.82 to 0.85 s, respectively. These data suggest that, in this case, the aggregation involves the ultimate CH_2 units of PVP: one from the chain and one from the ring. A decrease in the relaxation time can be associated not only with the aggregation in this mixture, but also with an increase in the solution viscosity.

The systems of GA and its SD with NCS were also studied. Thus, the analysis of the systems GA/SD of the NCS/GA (1:9) composition (Fig. S2B in the ESI) revealed that the signals at 8.3, 7.3, 4.3, and 4.0 ppm appeared to be slightly upfield shifted upon addition of NCS, while the other signals in the ^{1}H NMR spectrum remained unchanged. This means that, for these positions, the magnetic environment and nuclear configuration remained unchanged with the addition of NCS. The relaxation times T_2 of the protons with the downfield signals in the ^{1}H spectrum decreased slightly, while the relaxation times T_2 of the protons with the upfield signals showed a more significant decrease (from 0.15 to 0.13 s, from 0.21 to 0.13 s, from 0.29 to 0.16 s). This means that the aliphatic structural units of GA have a higher probability of interaction with the NCS molecule, while the protons of the aromatic moieties with the signals at 8.3, 7.7, and 7.2 ppm revealed the smallest change in the relaxation times T_2 and, therefore, practically do not participate in complex formation.

A similar pattern was observed for the system Na_2GA/SD of the NCS/Na_2GA (1:9) composition. A decrease in the relaxation times T_2 in this case also indicated complex formation in the system.

A somewhat different pattern was observed in the system AG/SD of the NCS/AG (1:9) composition (Fig. S2D in the ESI). Almost all the signals in the range of chemical shifts from 4.12 to 4.71 ppm, attributed to AG, did not reveal any significant downfield shift upon addition of NCS. At the same time, there was observed a downfield shift of the signals at 2.50–3.32 ppm. In this case, the proton relaxation times T_2 increased for the signals at 2.44–3.72 ppm and reduced for those with δ = 1.28–2.03 ppm. This most likely indicates that, in this case, the aliphatic groups of GA are predominantly involved in the processes of complex formation.

The analysis of the system PVP/SD of the NCS/PVP (1:9) composition showed (Fig. S2E in the ESI) that almost all the PVP proton signals in the spectrum appeared to be downfield shifted upon addition of NCS. At the same time, the relaxation time T_2 increased for the proton signals in the range of 2.44–3.72 ppm and decreased for the proton signals in the range of 1.28–2.03 ppm. This suggests that, most likely, the ultimate CH_2 units of PVP are involved in this SD: one from the chain and one from the ring.

The results of the NMR spectroscopic analysis confirmed the formation of supramolecular complexes of niclosamide with the polysaccharides explored and PVP.

The SEM studies revealed significant micronization of the

NCS and polymer particles upon their mechanical treatment, in particular, crushing of the spherical polymer particles (2–300 μm) in the NCS/PVP system with a decrease in the average size of PVP particles with an increase in the duration processing (39 μm for 1 h, 25 μm for 2 h, and 19 μm for 3 h) (see Fig. S3 in the ESI). At the same time, the NCS phase of acicular morphology retained the average size of the observed aggregates (5 μm) located on the surface of the PVP particles.

The polysaccharide polymers used in this work significantly differ in the particle sizes and morphology. AG (3–150 μm) has predominantly whole spherical particles, while Na_2GA (0.5–70 μm) almost half consists of crushed particles, which can be seen in Fig. S4 in the ESI. The mechanical treatment of a mixture of NCS with AG (with an average particle size of 10 μm) for 7 h led to the aggregation of the NCS acicular phase, resulting in discernable clusters, which is probably associated with the more hydrophilic nature of this polymer. In the case of the NCS mixture with Na_2GA (with an average particle size of 7 μm), a similar acicular phase of NCS was almost absent, which allows us to conclude that its grinding degree is significantly higher than those for the systems with AG and PVP.

The results of cytotoxicity studies of NCS and its SDs with the polymers are summarized in Table 2. Both NCS and its SD with the polymers exhibited remarkable cytotoxic effects against the tumor cell lines explored, with almost the same values of IC_{50} (the concentration required for 50% inhibition of cell growth). Of particular note is their selectivity towards different tumor cultures. Thus, the cytotoxic activity of the SDs with the polymers against colon cancer cells HCT116 was about 10 times higher than that against lung carcinoma cells A549. This means that the earlier known selectivity of NCS is also characteristic of its solid dispersions with polymers.

Table 2. Cytotoxicity of niclosamide and its SDs with the polymers

Sample and its composition	IC_{50} (μM)	
	A549 (human lung cancer)	**HCT116** (human colon cancer)
NCS	10.76 ± 0.39	1.65 ± 0.09
Na_2GA	79.43 ± 2.16	45.24 ± 1.21
SD of the NCS/Na_2GA (1:9) composition, 3 h of MT	15.95 ± 1.36	1.73 ± 0.01
SD of the NCS/Na_2GA (1:9) composition, 6 h of MT	18.66 ± 1.02	2.11 ± 0.02
SD of the NCS/GA (1:9) composition, 6 h of MT	11.73 ± 0.97	1.88 ± 0.03
SD of the NCS/PVP (1:9) composition, 6 h of MT	20.31 ± 2.69	1.58 ± 0.01
AG	– (no effect)	– (no effect)
SD of the NCS/AG (1:9) composition, 6 h of MT	11.47 ± 0.93	2.02 ± 0.08
Camptothecin	8.87 ± 0.02	12.34 ± 0.50
Daunorubicin	0.51 ± 0.01	0.24 ± 0.01
Doxorubicin	0.53 ± 0.02	0.19 ± 0.01

Experimental section

The investigations were concerned with the following substances and polymers: niclosamide (NCS) (5-chloro-*N*-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide) (Ghangzhou Yabang-Qh Pharmachem, China; batch no. 61014102), polyvinylpyrrolidone (PVP) (1-ethenylpyrrolidin-2-one, K-15) (Boai NKY Pharmaceuticals, China, batch no. P160828002-0), arabinogalactan (AG) (Levitol-arabinogalactan, *TU* (Specifications) *9325-008-70692152-08*; Ametis, Russia), glycyrrhizic acid (GA) (20-*β*-carboxy-11-oxo-30-norolean-12-en-3*β*-yl-2-O-*β*-D-glucopyranosyl-α-D-glucopyranosiduronic acid) (Shaanxi Pioneer Biotech, China), and a disodium salt of glycyrrhizic acid (Na_2GA) (Shaanxi Pioneer Biotech, China).

The solid dispersion of niclosamide with GA was synthesized according to the published procedure [3]. An LE-101 roller mill was sequentially charged with NCS (5.0 g), GA (45.0 g), and 810.0 g of milling balls. After preliminary agitation, the mechanical treatment was continued at a rotation rate of 60–70 rpm. The samples of solid dispersions were taken to analyze the changes in the solubility of NCS in time. The final product in the form of 48.5 g of a free-flowing beige powder was the target SD of the NCS/GA (1:9) composition.

The following SDs were obtained analogously:

– 47.8 g of the SD of the NCS/PVP (1:9) composition in the form of a light greenish free-flowing powder;

– 49.1 g of the SD of the NCS/Na_2GA (1:9) composition in the form of a free-flowing beige powder;

– 48.9 g of the SD of the NCS/AG (1:9) composition in the form of a light brown free-flowing powder.

The SDs based on NCS and PVP showed high anthelmintic activity [3]. The investigations on the solubility of the SDs based on the NCS/PVP (1:5; 1:10, and 1:20) compositions confirmed an increase in the solubility of NCS in 11.0, 19.0, and 26.7 times, respectively, which was explained by the lipophilic properties of the polymer. These results render further bioactivity studies very promising, since the solid dispersions of substances are considered as their new dosage forms and they are already used in medical practice [18, 19]. The investigations performed in this work were devoted to expanding the range of polymeric compounds (polysaccharides) used to modify the substance of niclosamide, as well as to the search for new types of biological activity of the resulting compositions.

The solubility of the resulting solid dispersions was determined by the amount of niclosamide in the filtrate obtained after stirring a sample of this dispersion in water for 3 h by high-performance liquid chromatography (HPLC) on an Agilent 1100 chromatograph with a Hypersil HyPURITY™ Elite C18 column (150×4.6 mm, 5μ); column temperature +30 °C; diode array detector. An acetonitrile/acetate buffer with pH = 3.4 (75:25) was used as an eluent, the flow rate was 1 mL/min, and the sample volume was 5 μL [3]. The quantitative determination (in mg/L) of dissolved NCS was performed by comparing the areas of NCS of the original substance and the SD (for example, NCS/GA). Taking into account the concentration of NCS in the original substance (in mg/L), the concentration of NCS in this SD was calculated.

The IR spectra were recorded on a VERTEX 70v FTIR-spectrophotometer (BRUKER, Germany) in the attenuated total reflection (ATR) mode using a Pike GladiATR adapter with a diamond crystal in the range of 4000–400 cm^{-1} with spectral resolution of 4 cm^{-1}. The spectra were obtained directly from the powder samples without their preliminary treatment. The measured ATR spectra were corrected using OPUS7 software to take into account the wavelength dependence of the penetration depth of IR radiation into the sample.

The LC–MS analysis was carried out on a Shimadzu LCMS-2020 instrument with electrospray ionization and a single quadrupole mass detector. A Shim-pack GIST 3 μm C18 3×150 mm column and a Shim-pack GIST (G) 5 μm C18 4×10 mm guard column were used as a stationary phase. Elution was performed in an isocratic mode with a mixture of 70 vol % of acetonitrile (99.9+%, HPLC grade, ChemLab) and 30 vol % solution of formic acid (0.1 vol %) in water (Milli-Q), flow rate 0.6 mL/min. The temperatures of the column oven, heating block, and desolvation line were 40 °C, 400 °C, and 250 °C, respectively. Nitrogen (99.999%) was used as a drying and nebulizing gas; the flow rates were 15 and 1.5 l/h, respectively. The electrospray voltage was 4.5 kV. The mass ranges from 100 to 1000 were scanned for positive and negative ions. The weighed samples in the amount of 0.2–0.8 mg were dissolved in 1 mL of methanol. If a suspension was formed, the samples were centrifuged. The external standard method was used to quantify NCS in the resulting SDs. For data analysis, LabSolutions and Microsoft Excel software were used.

The NMR studies were carried out on Bruker Avance IIIHD 500 and Varian Inova Unity 400 NMR spectrometers. The operating frequencies on ^{1}H nuclei were 500.13 and 400.11 MHz, respectively. The standard CPMG sequences were used to determine relaxation times T_2 [17]. For this purpose, the solutions of the compounds under consideration (complexes, mixtures of compounds) in D_2O at 298 °K were used. To prepare solutions, a sample of 2–5 mg of the drug was taken and dissolved in D_2O.

The SEM images of powder samples placed on a 25 mm aluminum stage and fixed with a conductive carbon tape were obtained in the secondary electron mode at an accelerating voltage of 15 kV and in a weak vacuum mode on a Hitachi TM4000Plus desktop electron microscope.

Human A549 (lung carcinoma, ATCC®CCL-185™) and HCT116 (intestinal carcinoma, ATCC®CCL-247™) cell cultures were grown in DMEM supplemented with 10% fetal bovine serum, 2mM L-glutamine, and 1% gentamicin as an antibiotic at 37 °C and 5% CO_2 in a humid atmosphere.

The *in vitro* cytotoxicities of the resulting SDs were determined using the conventional MTT test. Cells were seeded at a concentration of 1×10^4 cells/200 μL in a 96-well plate and cultured at 37 °C in a humidified atmosphere with 5% CO_2. After 24 h of incubation, various concentrations of the tested preparations were added to the cell cultures (from 100 to 1.56 μM/L in terms of the active substance) and then the cells were cultivated under the same conditions for 72 h. Each concentration of the tested substances was studied in triplicate. All the drugs explored were dissolved in DMSO; the final concentration of DMSO in the well did not exceed 0.05% and was not toxic to cells. The tested compounds were dissolved in DMSO. The control wells (cell culture in a nutrient medium without the tested substances) were supplemented with 0.05% DMSO compound solvent (0.1 μL DMSO per 200 μL well contents). After incubation, 20 μL of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide, 5 mg/mL) was added to each well, and the plates were incubated for another 2 h. Then the culture medium was removed from the plates, and 100 μL of DMSO was added to each well to dissolve the resulting formazan crystals. Mitochondrial oxidoreductases of living cells are able to reduce tetrazolium MTT into insoluble purple formazan, which remains in the wells in cells even after replacement of the culture medium for DMSO, dissolves in the latter with the formation of a purple color, the intensity of which is proportional to the number of living cells in the well. Using a Cytation3plate analyzer (BioTek Instruments), the cell viability was determined by measuring the optical density at 536 nm. The concentrations that afford 50% inhibition of cell growth (IC_{50}) were determined from the dose-dependent curves using OriginPro 9.0 software.

Conclusions

In order to improve the solubility of the niclosamide substance and to study the possibility of expanding its biological activity, the modification of NCS with various polymers was continuously explored. It was shown that the resulting SDs have increased solubility up to 52 times compared to the initial NCS. The highest increase in the solubility was observed in the case of the SD based on GA and its sodium salt, which are known to form micellar systems with improved solubility and bioavailability with drugs [14, 15]. The physicochemical properties of the products of the NCS mechanochemical modification were analyzed by means of HPLC, LC–MS, IR, NMR, and SEM. The results obtained confirmed that these SDs are finely dispersed powders that form supramolecular complexes in water. It was demonstrated that NCS does not undergo chemical degradation when it is mechanically treated with the polymers.

The solid dispersions of NCS exhibit the same level of cytotoxic activity as initial niclosamide against human lung and colon cancer cells, which is comparable to that of camptothecin. Furthermore, selectivity observed in the case of niclosamide is also characteristic of its complexes with the polymers. Thus, colon cancer cells HCT116 appeared to be more sensitive to them than lung cancer cells A549.

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Corresponding author

* E-mail: khalikov_ss@ineos.ac.ru (S. S. Khalikov)

Electronic supplementary information

The results of IR spectroscopic analysis of the chemical stability of niclosamide in its solid dispersions with the polymers; the NMR spectra and SEM images. For ESI, see DOI: 10.32931/io2221a

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