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Mechanochemically synthesised supramolecular Drug Delivery Systems

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Abstract

Physicochemical and pharmacological properties of mechanochemically synthesised supramolecular systems/complexes of the guest-host type have been studied at the institutes of the Siberian Branch of the Russian Academy of Sciences in cooperation with Chinese Zhejiang University of Technology. The guest is a molecule of a medicinal substance, and the host is a carrier particle – a macromolecule of polysaccharide, saponine micelle, silicon dioxide particle, etc. The strengthening of the pharmacological effect of such structures is achieved by increasing the water-solubility and trans-membrane permeability of drug molecules. The most effective hosts among the studied carriers are plant metabolites – glycyrrhizic acid and its salts, as well as polysaccharide arabinogalactan from *Larix Siberica* wood. An original solid-phase mechanochemical technology has been developed to obtain water-soluble supramolecular systems from the solid dispersions of components. In this case, supramolecular systems are formed in the process of solid-phase synthesis, or by dissolving the obtained dispersions in aqueous media. As a result of studies of a large number of widely used drugs of various pharmacological classes, it has been shown that the inclusion of drug molecules in these supramolecular systems can significantly increase the bioavailability, effectiveness and safety of their action and reduce the effective therapeutic dose of drugs significantly (by a factor of 2–150), and decrease (down to complete disappearance in some cases) harmful side effects. In this paper we give a brief overview of the studies carried out mainly over the last 10 years.

Keywords: drug delivery systems, mechanochemistry, bioavailability, solubility, intestinal absorption, solid dispersions

Механохимически синтезированные системы доставки биологически активных молекул

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Аннотация

Физико-химические и фармакологические свойства механохимически синтезированных супрамолекулярных систем/комплексов типа "гость – хозяин" изучались в рамках исследований институтов Сибирского отделения Российской академии наук в сотрудничестве с китайским Чжэцзянским технологическим университетом. "Гость" – это молекула лекарственного вещества, а "хозяин" – частица-носитель – макромолекула полисахарида, мицелла сапонинов, частица диоксида кремния и т. д. Усиление фармакологического действия таких структур достигается за счет повышения растворимости в воде и проницаемости молекул лекарственных средств через биологические мембраны. Наиболее эффективными "хозяевами" среди изученных переносчиков выступают растительные метаболиты – глицирризиновая кислота и ее соли, а также полисахарид арабиногалактан из древесины лиственницы сибирской. Для получения водорастворимых супрамолекулярных систем из твердых дисперсий компонентов была разработана оригинальная твердофазная механохимическая технология. В этом случае супрамолекулярные системы образуются в процессе твердофазного синтеза или путем растворения полученных дисперсий в водных средах. В результате исследований большого количества широко используемых лекарственных веществ различных фармакологических классов было показано, что включение их молекул в супрамолекулярные системы позволяет значительно повысить биодоступность, эффективность и безопасность их действия и значительно (в 2–150 раз) снизить эффективную терапевтическую дозу, а также уменьшает (вплоть до полного исчезновения в некоторых случаях) вредные побочные эффекты. В настоящей работе приведен краткий обзор исследований, выполненных в основном за последние 10 лет.

Ключевые слова: системы доставки лекарств, механохимия, биодоступность, растворимость, кишечная абсорбция, фармацевтические твердые дисперсии

Contents

INTRODUCTION

The Drug Delivery Systems (DDS) for biologically active molecules are widely used to improve the biopharmaceutical characteristics of already well known medicinal and other biologically active substances. For solid dosage forms, this is an increase in solubility and bioavailability, reduction of side toxic effects, and increased stability during storage. Due to the very high price and the long process of discovery, testing and registration of new drug molecules [1], the development and application of new delivery systems is a leading innovative direction in the global pharmaceutical industry.

The purpose of this mini-review is to summarize the data of recent years on the innovative solid-phase mechanochemical way of preparation, physicochemical properties and biological activity of solid dispersions of biologically active substances (BAS) with specially selected auxiliary substances that form various so-called delivery systems based on the physicochemical principle of inclusion of BAS molecules in intermolecular complexes formed by hydrophilic polymers, mainly of plant origin and vesicular systems formed also by plant saponins according to the type of guest-host interactions. Special attention will be paid to the advantages of the mechanochemical technology developed by the authors to produce water-soluble compositions of medicinal molecules. Increasing water solubility and intestinal absorption is very important for the medicinal substances of groups II and IV according to the FDA (Food and Drug Administration) classification [2]. At the same time, although BAS exhibit pharmacological/biological effects in aqueous solutions/physiological media, the properties of such solutions are largely determined by the composition and structure of soluble solid dispersions, which are actually powdered multicomponent materials.

The most frequently used auxiliary substances are plant polysaccharides and their derivatives, which are capable of forming intermolecular complexes with lipophilic BAS. However, in our experience, it is more effective to use vegetable saponins based on glycyrrhizic acid (GA) and its derivatives, in particular sodium salts. In this case, BAS molecules are incorporated into the micelles of these saponins formed during dissolution.

The above-mentioned issues were partially described in our previous works [3–5].

THE MECHANOCHEMICAL WAY OF OBTAINING SOLID DESPERSIONS

The subject of mechanochemistry of solids is the study of transformations of these substances under the influence of high pressure and deformations. There are many designs of devices in which the conditions for mechanochemical transformations are created. The most popular of them are mills for “dry” grinding of solids. However, mechanical processing is not limited only to material grinding. The transformations of solids in mechanochemistry are very diverse. Approximately, in the case of solid organic materials, the process can be represented in the form of the scheme in Fig. 1 [4, 6].

This process can be divided into several stages: grinding – aggregation – mixing of components at the molecular level. One can see that

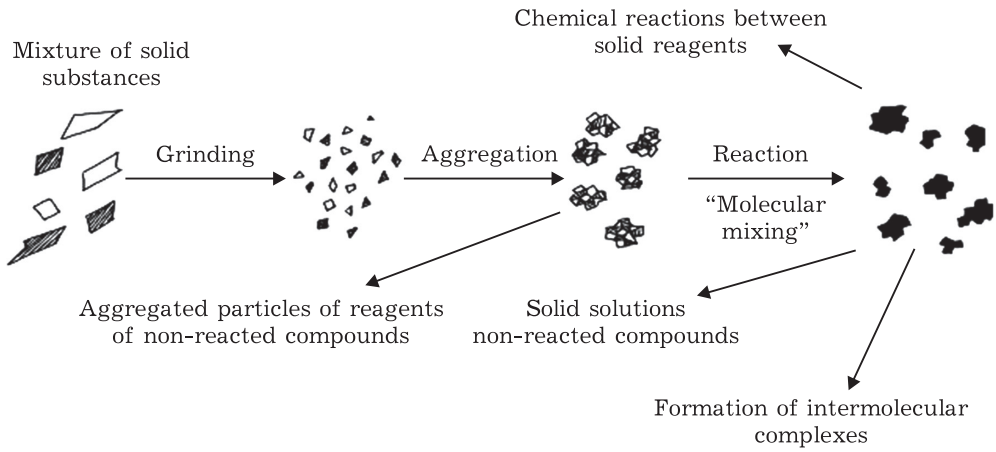

Fig. 1. The transformations of solids in mechanochemistry [4, 6].

grinding is only the first stage, then the crushed particles are "knocked down" into aggregates, and with continued mechanical activation, a kind of molecular mixing of solids occurs. Depending on the nature of substances, chemical reactions may occur or solid phases may be formed, in which their molecules enter into various kinds of interactions. As a result, at the stages of aggregation and even "molecular mixing", a composite material is obtained, so that each particle in its powder is an aggregate of ultrafine particles of the solid reagents and reaction products. During mechanochemical processing, all these stages take place almost simultaneously. They can be traced by scanning electron microphotography (SEM). The process of forming new particles comes to an equilibrium/stationary state as machining continues. Of particular interest are powder materials, mainly consisting of the aggregates of particles of starting substances. In our case, when they are hydrated during dissolution, the complexes and vesicles with the molecules of low molecular weight compounds – biologically active substances – are rapidly formed in solution.

In pharmaceutical chemistry, it is customary to describe such composite materials as pharmaceutical solid dispersions (PSD), see, for example, [7].

A number of methods for obtaining them are described. The authors of this article, based on their experience, believe that the "dry" mechanochemical technology has a number of undeniable advantages proven by the practice of use. These advantages include the absence of solvents and liquid phases (melts), the possibility for the processes to be carried out in one stage, the possibility of obtaining substances that do not have any areas of joint solubility in various solvents, and increased chemical stability of components in the production process.

PHYSICOCHEMICAL METHODS OF INVESTIGATION OF THE OBTAINED MATERIALS OF MIXED COMPOSITION

Scanning electron microscopy

This method allows us to trace the change in the size of solid particles during their grinding and the formation of aggregates – in fact, the formation of PSD.

Figure 2 shows electronic micrographs of both the initial components and the products of mechanochemical processing using a number of substances as examples [8].

Thermal analysis — differential scanning calorimetry

This method allows one to control the degree of the loss of crystallinity – the destruction of the crystal lattice of crystalline components, manifested in the reduction of the endothermic peaks of crystalline component melting until they disappear, which means amorphisation of phases or the formation of solid solutions [8]. Figure 3 shows the DSC (differential scanning calorimetry) thermograms of free and mechanically treated nimesulide, physical mixtures with polysaccharide arabinogalactan, and the formed solid dispersions.

The DSC curves of free nimesulide exhibited endothermic peaks at about 150 °C with melting heat value of 191.5 J/g, which corresponded to its

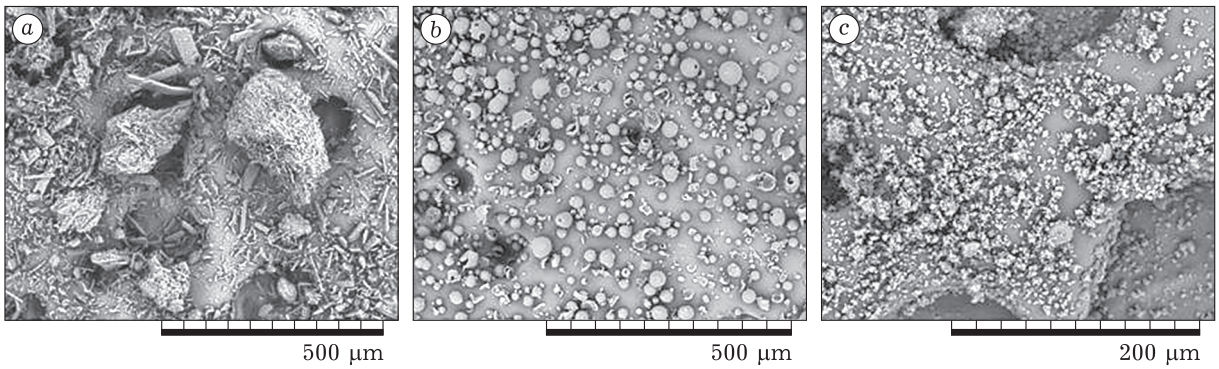

Fig. 2. Microphotographs of PZQ (*a*); Na_2GA (*b*), mechanochemically prepared composition PZQ/Na_2GA (1 : 10 mass relations) (*c*).

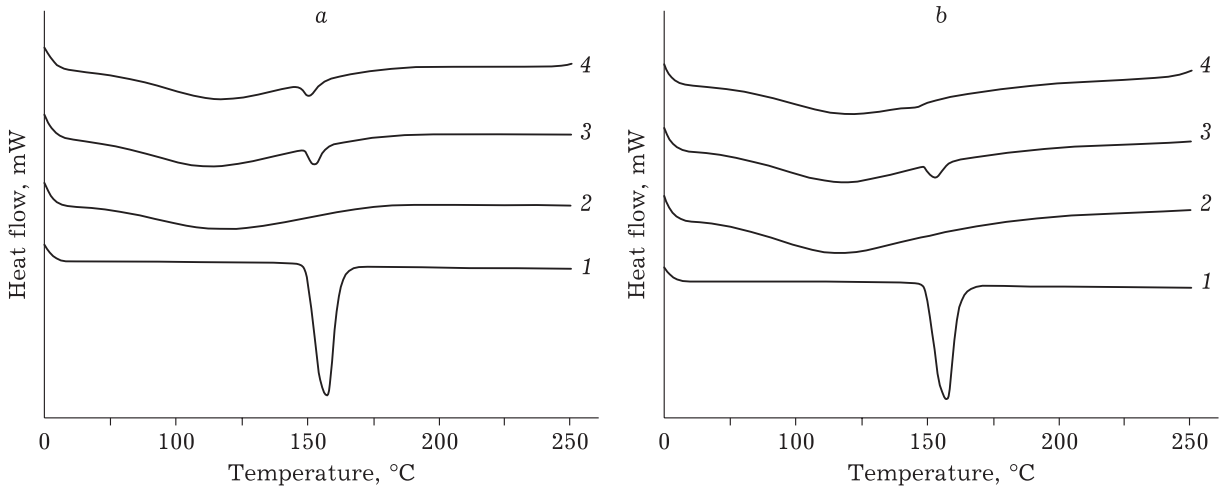

Fig. 3. DSC thermograms of: *a* – NIM API (*1*), AG (*2*), NIM/AG (1 : 10 mass relations) physical mixture (*3*) and solid dispersion of NIM/AG (1 : 10 mass relations) treated in roll mill for 24 h (*4*); *b* – NIM API (*1*); Na_2GA API (*2*), NIM/Na_2GA (1 : 10 mass relations), physical mixture (*3*) and solid dispersion of NIM/Na_2GA (1 : 10 mass relations) treated in roll mill for 24 h (*4*).

intrinsic melting points and suggested its highly crystalline structure. The endothermic peak of mechanically treated nimesulide without excipients is practically unchanged. However, the intensity of nimesulide peak decreased significantly in its solid dispersion obtained after milling for 2 to 24 h, while melting heat values decreased from the initial value to a minimum, which is difficult to calculate, indicating that nimesulide had converted to a mainly amorphous state and probably was partly dispersed in the molecular form in the bulk phase of organic carrier during the mechanochemical process.

X-Ray diffraction

This is a structural method that also allows one to determine the degree of crystal structure preservation in the components.

Figure 4 shows X-ray diffraction patterns of free curcumin, the excipient disodium salt of glycyrrhizic acid, a physical mixture, and a solid dispersion with curcumin to excipient molar ratio of 1 : 1, 1 : 2, 1 : 4 and milling time of 8 and 24 h. These data demonstrate a decrease in crystal size through mechanical transformation [9].

High-performance liquid chromatography

To analyse the content of medicinal substances, high-performance liquid chromatography (HPLC) was used in the reversed-phase version. Eluents are buffered mixtures of organic solvents – acetonitrile, isopropyl alcohol and bidistilled water in different ratios. The detector is spectrophotometric. Analysis methods were based on the conditions given in various articles of the United States Pharmacopoeia for the relevant substances. During the mechanochemical preparation of solid dis-

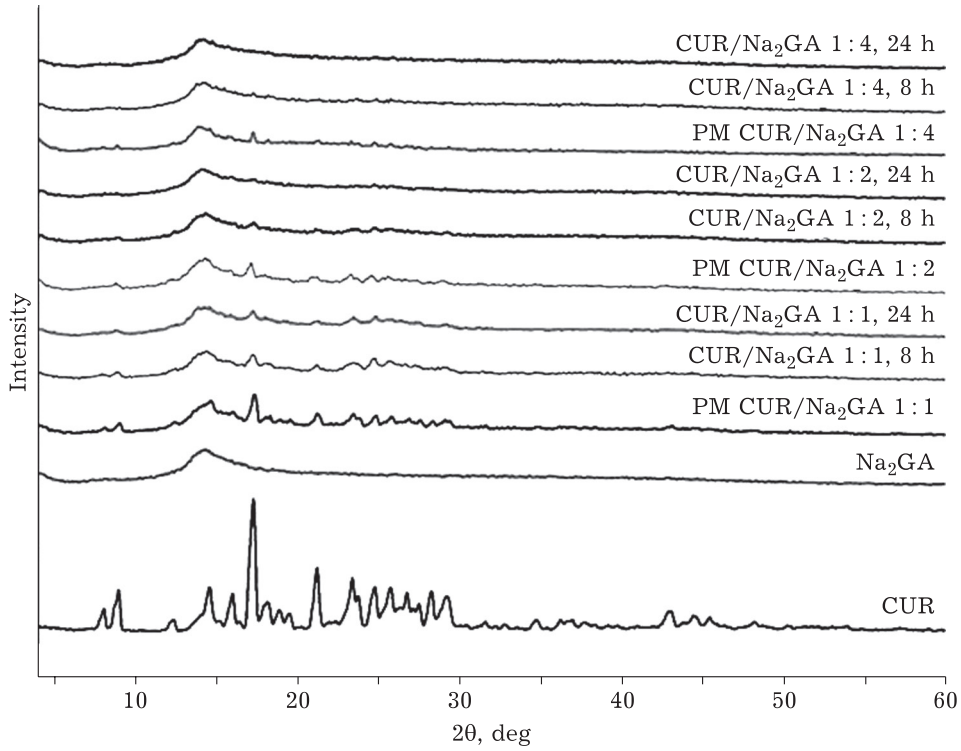

Fig. 4. X-Ray diffractograms of free CUR, excipient Na_2GA, physical mixture (PM), and solid dispersion with CUR/Na_2GA molar ratio of 1 : 1, 1 : 2, 1 : 4 and milling time of 8 and 24 h.

persions, the conditions of mechanochemical treatment were chosen in order to avoid the destruction of the starting substances, as well as their chemical interaction. The accuracy of the analyses was not worse than 1 %.

Gel chromatographic measurements

Gel chromatographic measurements were carried out to assess the molecular weight distribution and sizes of supramolecular formations of adjuvant solutions – the macromolecules of polysaccharides and micelles of saponins, as well as their complexes with medicinal substances. The detector is refractometric. Certified dextran samples were used as standards [10].

Laser scattering

To estimate the size of supramolecular formations, laser light scattering method was also used, with a Photocor Complex multi-angle particle size analyser, which allows determining the particle size from 0.5 nm to 10 μm [11].

Determination of the solubility of medicinal substances and their complexes

In our experiments, so-called phase solubility was determined, in the case when all the substances of the resulting composition, both in the solid phase and in solution, are in equilibrium. This is illustrated in Scheme 1.

$$\text{Drug (solid)} \longleftrightarrow \text{Drug (solution)}$$
$$\text{Drug (solution)} + \text{Lg} \longleftrightarrow \text{(Drug/Lg) complex (solution)}$$
$$\text{(Drug/Lg) complex (solution)} \longleftrightarrow \text{(Drug/Lg) complex (solid/rest)}$$
$$C_{\text{drug}}\ \text{(total in solution)} = C_{\text{complex}} + C_{\text{drug (solution)}}$$
$$\text{Lg} - \text{complexation agent}$$
$$\text{Increasing of solubility:}$$
$$X = 1 + (C_{\text{complex}}/C_{\text{drug (solution)}})$$

Scheme 1. Scheme of solid-liquid equilibrium during dissolution of mechanochemically obtained compositions.

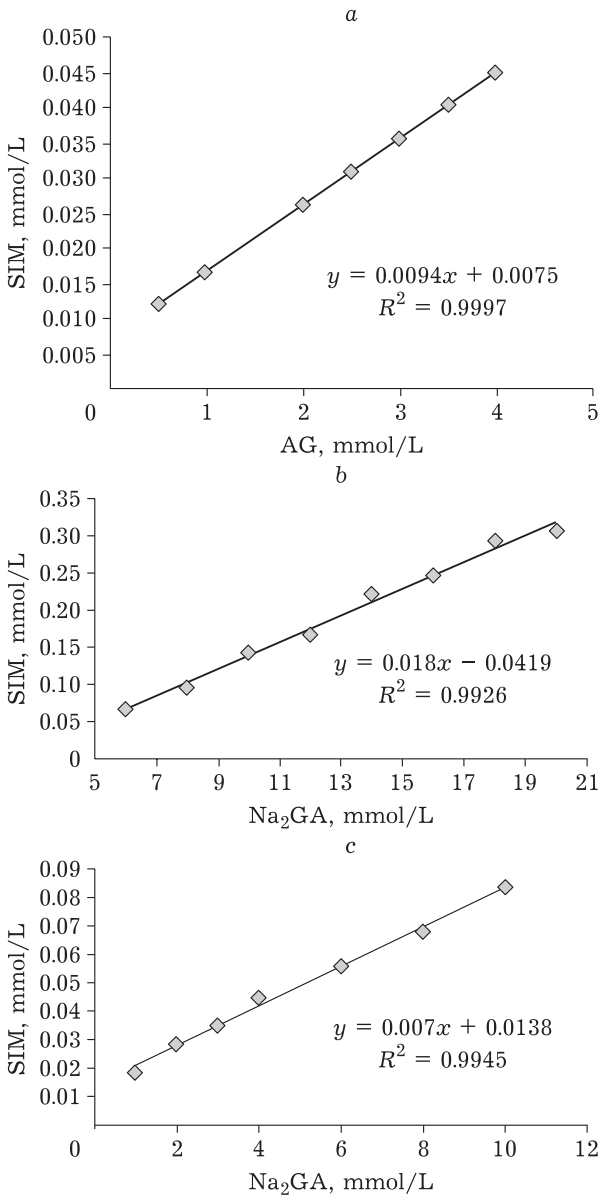

Fig. 5. Phase solubility diagrams of complexes simvastatin: SIM/AG (1 : 10, mass relations), SIM/Na_2GA (1 : 2, mass relations) and SIM/Na_2GA (1 : 4, mass relations) at 37 °C in aqueous solution [13] and calculated stability constants.

Here drug is an active pharmaceutical ingredient; Lg is a complex-forming supramolecular system, which is either a polymer macromolecule or saponin micelle; *X* is an increase in solubility of drug in water. In our experience, *X* varies from values >1 to several thousands, depending on complexation affinity.

TABLE 1

Association constants (*K*) of complexes SIM with AG or Na_2GA at 37 °C

Composition	*K*, L/mol	ΔG, KJ/mol
SIM/AG (1 : 10, 2 h)	1274.0±35	−18.4±0.17
SIM/Na_2GA (1 : 4, 4 h)	437.8±93	−15.7±0.5
SIM/Na_2GA (1 : 2, 4 h)	525.5±55	−16.1±0.3

Phase diagrams of solubility

We used the method described in [12] to evaluate the stability constants of complexes between drug molecules and polymer macromolecules or micelles. As a rule, the resulting diagrams provide evidence of the formation of a stoichiometric 1 : 1 complex of simvastatin (SIM) with disodium glycyrrhizinate (Na_2GA). Figure 5 shows phase solubility diagrams of SIM complexes [13].

Table 1 presents the calculated stability constants.

Trans-membrane permeability on artificial membranes (PAMPA)

The Parallel Artificial Membrane Permeability Assay (PAMPA) enabled fast determination of the trends in the ability of compounds to permeate the membrane by passive diffusion and thus was suitable for screening potential drugs [14–17].

In our case, we try to provide similar experiments to choose appropriate compositions for tests *in vivo*. Simultaneously, we make experiments using chemical artificial membranes (hexadecane) as well as cells monolayers (Caco-2).

Figure 6 shows the rate of nimesulide permeability from the initial pharmaceutical agent and its solid dispersions with different excipients. In this case, PAMPA enabled different trends in the ability of the compounds to permeate membrane by passive diffusion and thus may be suitable for screening potential drugs.

In the plots (see Fig. 6), it can be seen that the amount of nimesulide from mechanochemically treated complexes permeated is higher than from the pure substance, as well as from its solid dispersion with $MgCO_3$, indicating that the co-grinding complexes with hydroxypropyl-β-cyclodextrin (HP-β-CD), arabinogalactan and disodium glycyrrhizinate have enhanced the permeation/flux/mass transport of nimesulide across an artificial membrane, compared to that of the pure drug.

Drug molecules encounter two types of resistance when they permeate through artificial membranes, i. e., membrane resistance in the lipophilic membrane and diffusion resistance in the unstirred water layers adjacent to surfaces of the lipophilic membrane. Earlier it was found that

hydrophilic cyclodextrins could exert an improvement in drug permeation, which was associated with the ability of HP-β-CD to transport a drug molecule though the unstirred water layers so that it was brought in close proximity to the lipophilic membrane.

The low permeation of nimesulide from its solid dispersion with $MgCO_3$ through the artificial membrane seems slightly surprising, because it has the highest solubility, which is more than 10 times higher than from other solid dispersions. The only reasonable explanation is that in this case an increase in solubility is reached by ionization and salt formation, and more hydrophilic and charged membrane forms of NIM molecules cannot be accepted by hydrophobic membrane [15].

Nuclear magnetic resonance spectroscopy in liquid state

Nuclear magnetic resonance (NMR) spectroscopy is one of the most sensitive physical methods for the studies of weak non-covalent intermolecular interactions. This method can provide useful information on many aspects of drug delivery, such as monitoring drug encapsulation, drug release, and stability of carrier systems. Classical NMR spectroscopic methods such as NOESY (nuclear Overhauser effect spectroscopy) and DOSY (diffusion-ordered spectroscopy) are used to analyse drug localization, as well as exchange processes and release from the carrier in physiological solution [18, 19]. In our studies, we used the selective NOESY and NMR relaxation methods. The NOESY method makes it possible to determine the localisation and distribution of drug molecules in lipid membranes, as well as in inclusion complexes (micelles, polymer nanoparticles). Intermolecular cross-peaks in the NOESY experiment are observed at a distance of less than 0.5 nm between the protons [20, 21]. The NMR relaxation method is sensitive to the mobility of molecules in solution and is therefore widely used to demonstrate the formation of inclusion complexes. The essence of the experimental approach is to significantly reduce the mobility of a small molecule when it is incorporated into a micelle or polymer matrix. This leads to a significant, tens of times, increase in the T_2 relaxation rate [22–24]. As an example, Fig. 7 shows the results of measuring the T_2 relaxation time of ibuprofen in an aqueous solution and in a mechanochemically prepared complex with the polysaccharide arabinogalactan [25].

Molecular dynamics

Molecular dynamic (MD) simulations are widely used *in silico* to study drug delivery systems. The first way of MD application to drug delivery systems is the study of dissolution and solvation processes [26–29]. The second task which can be solved by the MD approach is the study of drug molecule complexation with delivery systems, characterisation of complex structures and dynamics including micelles, cyclodextrins and liposomal drug carriers [23, 30–33]. The third way of the application of MD simulations is to study the interaction of drug delivery system with lipid membranes, see for example [34, 35].

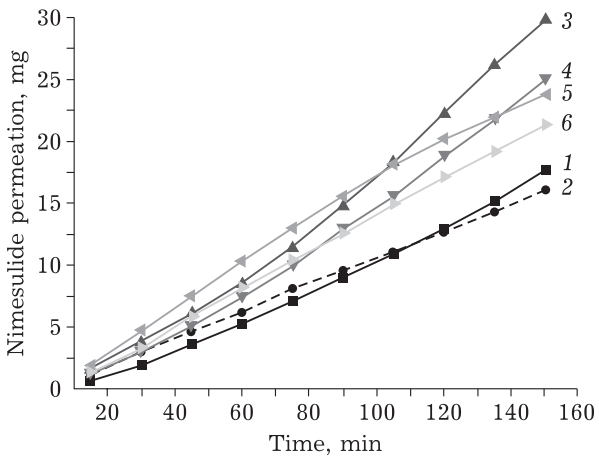

Fig. 6. Permeation profile of NIM (*1*) and complexes: NIM/$MgCO_3$ (5 : 1) (*2*), NIM/AG (1 : 10) (*3*), NIM/Na_2GA (1 : 1) (*4*), NIM/HP-β-CD (1 : 1, mol) (*5*), NIM/HP-β-CD (1 : 2, mol) (*6*).

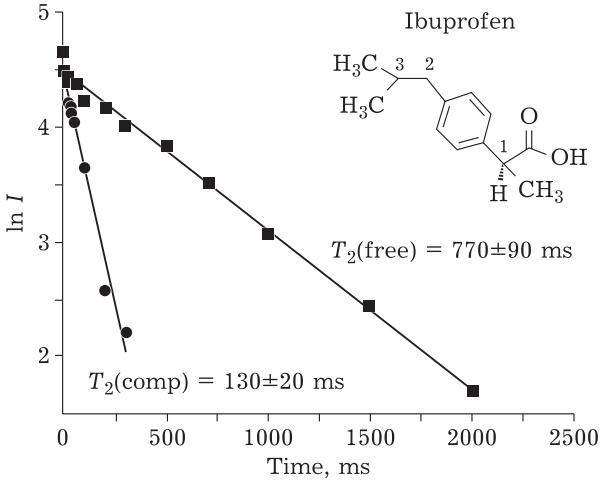

Fig. 7. Time dependences (in logarithmic scale) of NMR intensity (CPMG experiment) of 1-CH_3 protons of ibuprofen in phosphate buffer in free form and in the complex with AG (1 : 10, 10 g/L) at T = 25 °C. Adopted from [25].

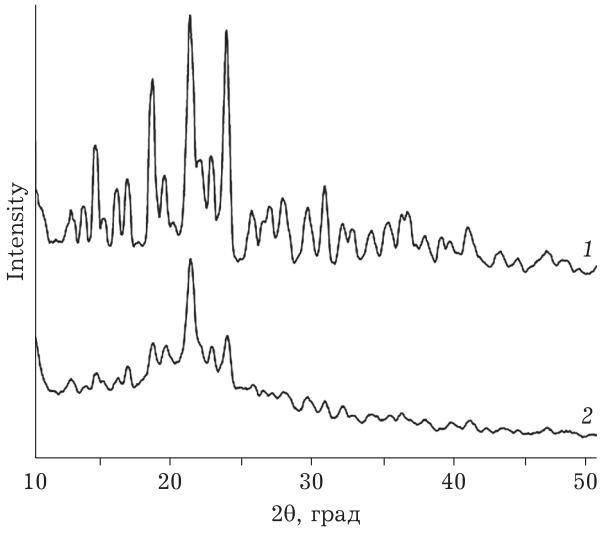

Fig. 8. X-Ray diffractograms of ceftazidime (*1*) and ceftazidime/polysorb (1 : 1) after mechanical treatment (*2*).

APPLICATION OF DIFFERENT SUPRAMOLECULAR CARRIERS

Amorphous silicium dioxide

Amorphous silicon dioxide (silica, polysorb) is a very popular inorganic material widely applicable in medicine, for example in enteric sorbents. It consists of particles 1–30 μm in size in water suspension, with a maximum at ~10 μm. In the dry state, we see that the observed large particles appear as aggregated with a size of 30–100 nm. The specific surface area is close to 300 m^2/g. Our idea was to obtain compositions with several cephalosporin antibiotics for taking medication by infusion. We used cephalosporin antibiotics: cefotaxim, ceftazidin, cefuroxime, cefoperazone, cefoxitin, cefepim, ceftriaxone and phosphomycin. In all cases we executed dry mechanochemical treatment of a mixture of a drug with polysorb in different ratios. The solid phases of antibiotics have a loose crystal structure. Figure 8 shows X-ray diffraction patterns of ceftazidime and ceftazidime/polysorb (1 : 1) after mechanical treatment.

Simultaneously, the absorption of antibiotics into the nanostructure of polysorb takes place, as well as a sufficient increase of the fraction of small-size <10 μm particles. Preparations were tested *in vivo* using laboratory mice infected preliminarily with different bacteria. Table 2 shows the survival of mice after infection.

One can see that the application of our preparations causes approximately 2-fold increase in the survival of animals. The possible mechanism is blood platelet-assisted transport of antibiotics/polysorb particles to the inflammation site in an animal. The results were published in patents [36–48], as well as in journal articles [49–55].

Supramolecular micelle structures for lipophilic molecules of active pharmaceutical ingredient

There are many natural saponins that can be used in medicine. From our point of view, glycyrrhizic acid its derivatives (salts) are of special interest as auxiliary compounds possessing low toxicity and forming supramolecular auto-associates. It has been proposed that glycyrrhizic acid molecules can form dimer structures possessing a hydrophobic cavity [56, 57]. Micelle formation was assumed in [58]. Nevertheless, the first direct detection of glycyrrhizic acid micelles was demonstrated in [59] by the size-exclusion high performance liquid chromatography (SE-HPLC) technique. It was shown that molecular weight distribution was relatively narrow, with low polydispersion degree, expressed as the weight-

TABLE 2

Survival of mice after infection

Investigational antibiotics and compositions	Survival in a group of 30 mice on the 7th day after infection, %		
	S. aureus	*E. coli*	*P. aeruginosa*
Saline solution (control)	0	0	0
Polysorb (control)	0	0	0
Cefotaxime	40.0	43.3	–
Cefotaxime/polysorb	86.7	83.3	–
Ceftriaxone	46.7	41.9	–
Ceftriaxone/polysorb	90.0	87.5	–
Ceftazidime	–	38.7	43.3
Ceftazidime/polysorb	–	84.8	86.7

average to number-average molecular weight (M_w/M_n = 1.08–1.06), but could change depending on the concentration of glycyrrhizic acid in solution within the range of 50–70 kDa, which corresponds to about 40–70 molecules of glycyrrhizic acid per micelle. Figure 9 shows SE-HPLC in water solution for different concentrations of glycyrrhizic acid.

It should be stressed that micelles are supramolecular structures that can incorporate hydrophilic molecules by host-guest type interaction. During mechanochemical preparation of solid dispersed systems, small molecules of pharmaceutical agents can be distributed in an excessive volume of adjuvant, losing their crystallinity and possibly forming a solid solution of isolated molecules. This is confirmed in our experiments on electron spin resonance (ESR) studying stable nitroxides. Figure 10 shows the results of the ESR study.

We see the starting solid phase of radicals, when there are neighbouring paramagnetic centres. So, electron spin-spin exchange interaction diminished the fine structures of ESR spectra [60, 61]. After mechanical treatment of solid substances, it is possible to form a homogeneous solid phase in which the molecules from different/micro crystal states can be distributed homogeneously.

There is a transformation from the condensed solid state of radicals to the spatially isolated state. This is actually a solid solution of radicals, obtained by solid mechanochemical technology. The radicals are only modelling systems. We propose that similar transformations be accrued with other active pharmaceutical ingredients (API) of organic nature and the low lattice energy.

It is important that during dissolution in water, auxiliary substances (saponins) simultaneously formed micelles with the incorporated molecules of pharmaceutical substances. So, this excludes consequent stages of dissolution of slowly soluble API and its transport/mixing and inclusion to earlier solvated saponin micelles.

We propose this process as a much more effective one than the liquid phase technology of components mixing [62].

Composition with polysaccharides

During the mechanochemical production of the solid dispersions of pharmaceutical substances, the processes similar in their nature to those described in the previous section occur. These processes include the loss of crystallinity, depreciation or formation of solid solutions, the formation of particle aggregates (see Fig. 1). However, the water-soluble polysaccharides studied by us have a branched structure and, in our opinion, are capable of forming intermolecular complexes in cavities formed by lateral branches. Figure 11 shows the proposed structure of arabinogalactan (AG) macromolecules isolated from *Larix sibirica* wood.

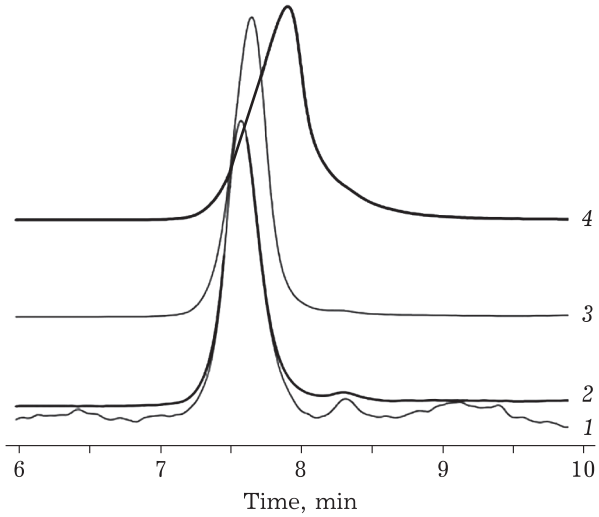

Fig. 9. SE-HPLC in water solution of GA in different concentrations, wt%: 0.001 (*1*), 0.01 (*2*), 0.1 (*3*), 0.5 (*4*).

Another feature of such branched macromolecules is the molecular mobility of the side chains, probably due to rotation around the C–O–C bonds connecting individual monosaccharides into a macromolecular structure. This phenomenon manifests itself when measuring the transverse T_2 relaxation times of protons in aqueous solutions, as well as in the solid state, when a relatively narrow spectrum component is observed even in the dried state. Figures 12 and 13 show the results of ^{1}H NMR study of arabinogalactan.

The nonlinear form of the dependence of the logarithm of intensity (ln I) on time indicates the presence of arabinogalactan fragments that differ significantly from each other in mobility (rotation correlation time), and, consequently, in spin-spin relaxation times. The decay kinetics of the NMR signal in a relaxation experiment is not described by one or two exponentials (see the inset in Fig. 12). Therefore, the analysis was carried out with a 3-exponential approximation. The solid curve in Fig. 12 is the result of fitting using a 3-exponential function: $I = A_1\exp(-t/T_1) + A_2\exp(-t/T_2) + A_3\exp(-t/T_3)$. The measured spin-spin relaxation times of protons in arabinogalactan are presented in Table 3.

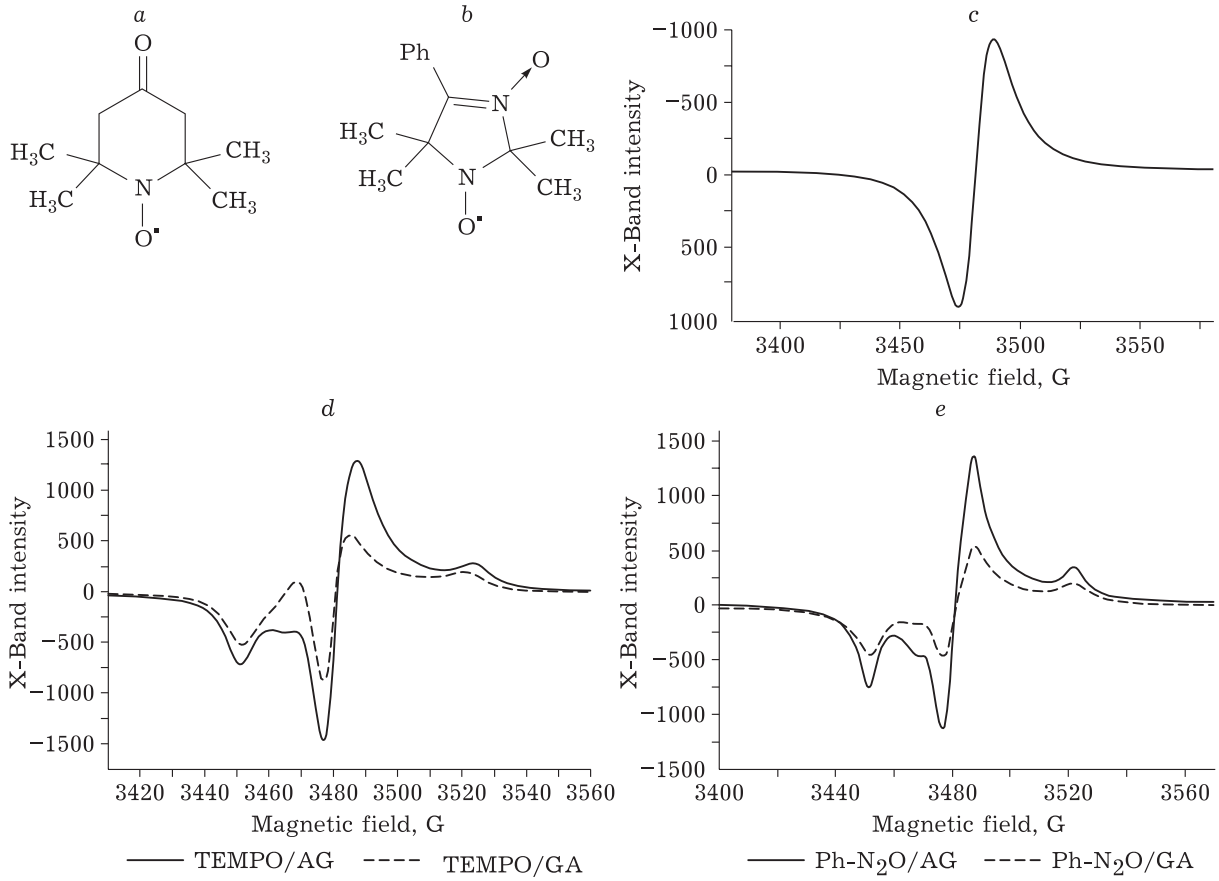

Fig. 10. Structure of nitroxyl radicals TEMPO (*a*), Ph-N_2O (*b*), electron spin resonance spectra of TEMPO (*c*), TEMPO mechanically treated with arabinogalactane (AG) and glycyrrhizic acid (GA) (*d*), Ph-N_2O mechanically treated with AG and GA (*e*).

It can be seen that various AG fragments are very heterogeneous in their mobility; both very mobile fragments with relaxation times of 200–300 ms and fragments with restricted mobility with relaxation times of 2–3 ms are present in approximately equal quantities.

The NMR spectrum of arabinogalactan powder has a typical appearance characteristic of the solid samples of polysaccharides and consists of a broad line related to the less mobile skeleton of the arabinogalactan molecule and water molecules tightly bound to it, as well as a narrow peak related to the mobile side chains of the polymer and weakly bound water molecules. An increase in temperature leads to narrowing of the broad line, which indicates an increase in the mobility of the carbon skeleton of AG macromolecule, as well as a narrowing and increase in the intensity of the narrow line, which may be a consequence of the transition of strongly bound water to a weakly bound state, as well as an increase in the proportion of mobile side groups with increasing temperature. At the same time, with a further increase in temperature in the range of 100–120 °C, a reverse broadening process occurs, associated with the evaporation of water. The loss of water leads to a significant decrease in the mobility of the side chains of arabinogalactan macromolecule.

The data obtained indicate the possibility of introducing pharmaceutical molecules into the cavities between the side chains even in the solid state under the conditions of severe mechanical deformation. Thus, it can be assumed that the intermolecular complexes of drugs with arabinogalactan macromolecules are formed during the direct mechanochemical treatment of their mixtures. An increase in water solubility of pharmaceutical substances from such complexes occurs according to Scheme 1. At the same time, various water-soluble polysaccharides are capable of forming complexes with different stability, which is reflected in the degree of an increase in drug solubility. In our experience, the most convenient polysaccharide is arabinogalactan isolated from *Larix Sibirica* wood. It is readily available and relatively cheap. Due to its relatively low molecular weight (14–16 kDa), it is little susceptible to mechanical destruction and does not form oligomers – undesirable impurities.

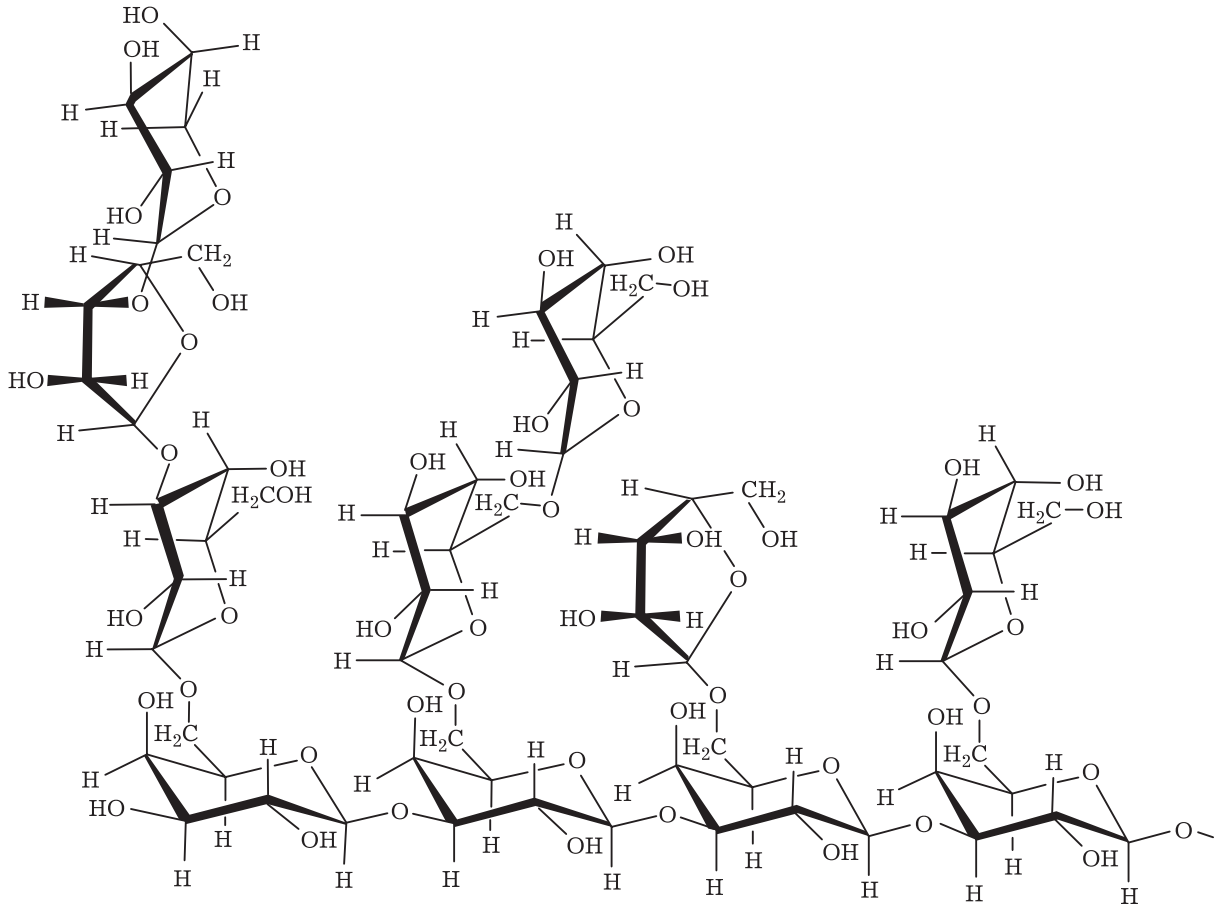

Fig. 11. Proposal structure of arabinogalactane (AG) macromolecules, isolated from wood *Larix sibirica*.

Molecular dynamic modelling

Molecular dynamic (MD) calculations are widely used *in silico* to study intermolecular structures. The simplest way of the application of MD to drug delivery systems is to study the processes of dissolution and solvation. Thus, the MD approach was applied to study the dissolution of drug molecules in complexes with solid dispersions [26–29]. The simulated annealing method

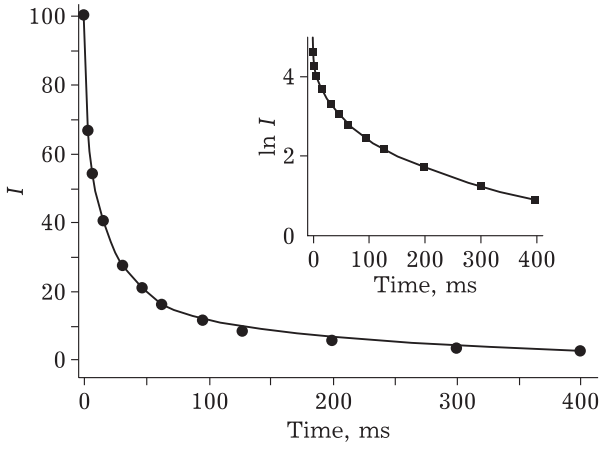

Fig. 12. Experimental measurement of spin-spin T_2 relaxation times of a 1 % aqueous solution of arabinogalactan (manufactured in Irkutsk) by ^{1}H NMR using a CPMG pulse sequence. In the insert – on a logarithmic scale. I – intensity.

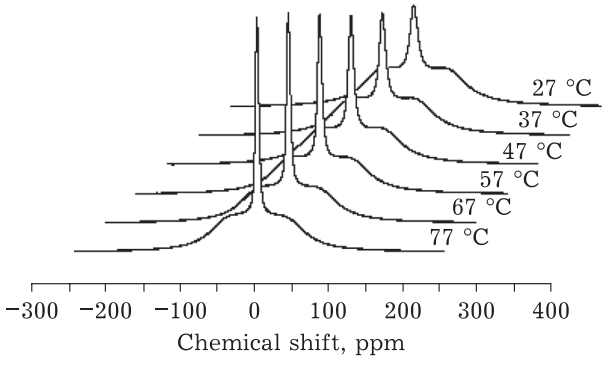

Fig. 13. ^{1}H NMR spectra of arabinogalactan in the solid phase at various temperatures.

TABLE 3

Spin-spin relaxation times (T_i) and relative intensities of contributions (A_i) of AG protons in a 1 % aqueous solution

A_1, %	T_1, ms	A_2, %	T_2, ms	A_3, %	T_3, ms
37±2	2.7±0.2	46±1.5	25±2	17±1.5	217±20

was used to prepare the solid dispersions in simulations. The computational results revealed molecule-related differences in dissolution behaviour in different solid dispersions [26, 27].

Another task which can be solved by the MD approach is the study of complex formation of drug molecule with delivery system and characterisation of complex structure and dynamics. Thus, it was shown that glycyrrhizic acid (GA) could form complexes with nifedipine molecules in water. Complexes could be formed in different protonation states of GA (fully protonated neutral GA molecule, GA^-, GA^{2-}, GA^{3-}) [23]. This approach was also used to study inclusion complexes of cyclodextrins with different drug molecules [30, 31]. The MD simulations provided a better understanding of molecular interaction between molecules in complexes. For example, for the lutein molecule it was found that it exists in host-guest complexes with β-cyclodextrin, γ-cyclodextrin, hydroxypropyl-β-cyclodextrin, but for α-cyclodextrin the complex stability is very low [31].

The MD simulations are also used to model the structure and dynamics of liposomal drug carriers [32, 33].

Another way of application of MD simulations is the study of interaction of a drug delivery system with the lipid membrane. Thus, the interaction of GA with lipid membrane was studied by means of molecular dynamics simulation in combination with different experimental techniques. It was demonstrated that GA molecule can penetrate into the lipid membrane and form self-associates within it [34, 35]. It was found that the ability of GA to penetrate through lipid bilayer depends on GA protonation state. In the fully protonated neutral state, it is able to penetrate into lipid bilayer, but in the charged states it is located on the bilayer surface [63]. It was revealed that GA-nifedipine complexes are able to penetrate through lipid bilayer without preliminary dissociation. Free energy calculation demonstrated that the permeability of lipid bilayer for drug molecules increases in the presence of GA [64, 65]. The obtained computational results are in good agreement with experimental data.

DRUGS BASED ON MIXED NANO-SCALE SYSTEMS

Currently, in the field of DDS, there is a tendency to use mixed delivery systems, so-called intelligent nano-delivery systems of bioactive compounds, which allow achieving maximum (optimal) effect in terms of increasing solubility, stability at different pH levels, controlled release, passage through cellular barriers and reaching a specific target [66, 67]. Below are a few examples of the application of such mixing DDS performed by our research groups.

Bearing in mind the long-term development of the mechanochemical synthesis of supramolecular systems – carriers of pharmaceutical substances, it is of practical and theoretical interest to create and study multicomponent supramolecular systems, which may have expanded the possibilities of the approach under study, due to a further increase in the basic biopharmaceutical parameters of the drugs obtained, as well as a decrease in the cost characteristics of auxiliary devices. It seems that the latter path is particularly relevant when creating feed additives for farm animals, and the interest has shown an extremely wide range of possibilities for increasing the solubility and bioavailability of veterinary drugs and feed additives. In addition, the same applies to the creation of chemical plant protection products, where the cost of drug components is an important factor. Anyway, the procedure that has been proved to be effective in improving the solubility and stability of unstable drugs, especially suitable for volatile and oily drugs, is liquification at room temperature. Through mechanochemical techniques, such kinds of pharmaceutical substances could be prepared directly in mixed nano-delivery systems under low temperature. For example, Zheng et al. developed an inositol hexanicotinate (IHN) self-micelle solid dispersion (IHN/GA/ArG SDs) [68] with glycyrrhizic acid (GA) and arabic gum (ArG) prepared by mechanical ball milling process. Pharmacokinetic study of this formulation in rats showed a significant 3.3-fold increase in bioavailability compared to pure IHN. Moreover, biomarkers in serum and liver of non-alcoholic fatty liver disease (NAFLD) mice were significantly ameliorated after oral administration of IHN/GA/ArG SDs for 15 days. Altogether, these results showed that IHN/GA/ArG SDs was an efficacious formulation for the treatment of hyperlipidemia and NAFLD. Aimed to overcome the problems [69] in the application of

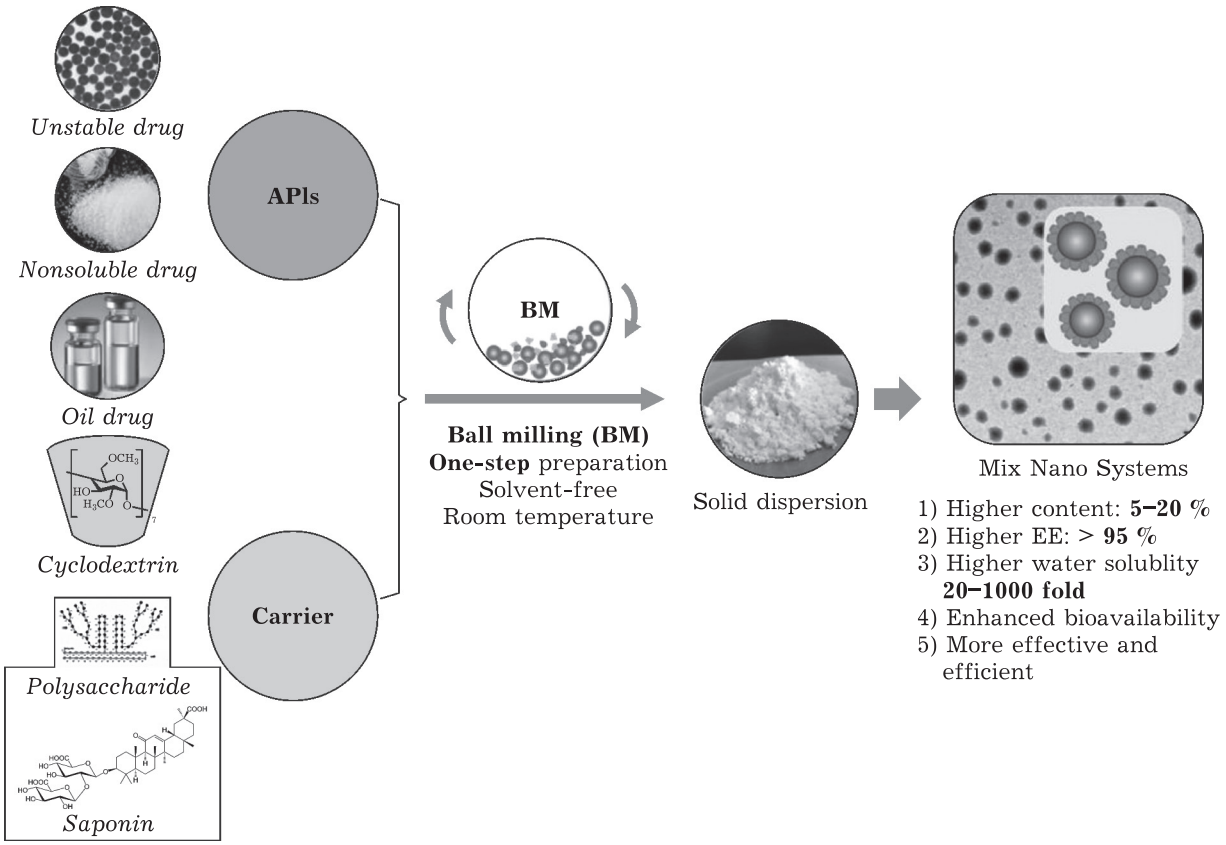

Fig. 14. Drugs based on mixed nano-scale systems.

nature carotenoids astaxanthin (AST), Su et al. [70] developed a mechanochemical method to prepare a micellar self-assembled inclusion complex (AST-IC). The based on related analysis AST, hydroxypropyl-β-cyclodextrin and glyceryl monostearate in AST-IC fully formed self-assembled micellar systems and maintained good stability in aqueous solution. Related experiments showed that AST-IC increased the free radical scavenging activity of AST and increased the bioavailability of AST to 4-folds, while AST-IC could also target the liver to exert its antioxidant effects. Xu et al. [71] use mechanochemical method to prepare celery seed oil/methyl-β-cyclodextrin nano capsule (CsNIs) as a mix nano delivery system. Results showed that CsNIs had high encapsulation efficiency (98.39 %), and had more stable antioxidant activity under sunlight exposure. The water solubility was improved by 30-fold. Celery seed oil/methyl-β-cyclodextrin nano capsule will self-assemble into nano-spheres in aqueous solution and be slowly released to 77.2 % in 48 h. Pharmacokinetic study also showed that after treating with CsNIs, the uric acid levels and the degree of renal injury were significantly lower in hyperuricemia (HUA) mice. Figure 14 shows drugs based on mixed nano-scale systems.

Mechanochemically prepared mixed nano-delivery systems have also been shown to improve the solubility and bioavailability of insoluble drugs and even realize the effect of targeted delivery, thereby reducing drug toxicity, e. g., Lu et al. [72] exploited an aqueous-soluble formulation 4,4′-dinitrocarbanilide/glycyrrhizic acid/polyvinylpyrrolidone K30 solid dispersion (DNC/GA/PVP K30 SD) possessing anticoccidial activity due to DNC (the active component of nicarbazin), prepared mechanochemically. An increase in the oral bioavailability (4.64-fold), tissue distribution, and anticoccidial activity of this solid dispersion was compared with the characteristics of the free drug. The dispersion will provide a good opportunity for treating coccidiosis. Wei et al. developed a protamine-hyaluronic acid coated core-shell decoquinate (DQ) nanoparticles (DQ-SD) [73] by using mechanochemical technology. Results showed that DQ-SD is easily generated via self-assembly in the aqueous phase to form nano-micelles consisting of disodium glycyrrhizinate nanoparticles with a protamine and anionic hyaluronic acid (HA) layers. The bioavailability of DQ-SD was approximately 6.3 times higher than that of pure DQ, and DQ-SD provided a significantly higher concentration in

the blood and preferential liver tissue accumulation than that of pure DQ.

For the treatment of ulcerative colitis, Xu et al. [74] developed a non-covalent polymer hydrogel of chitosan (CS) and sodium alginate (SA), and loaded 5-amino salicylic acid (5-ASA) synchronously by using the mechanochemical method, from the thermodynamics study, particle size analysis, and electron microscopy show that CS and SA form a pH-sensitive hydrogel under the mechanochemical force and also maintain good stability in aqueous solution. Fluorescent tracers study showed that the pH-sensitive hydrogel could achieve the targeted drug release in the colon and the retention time was over 12 h. Next, *in vivo* efficacy studies, change in mice body weight, DAI (disease activity index) score, thymus, and spleen index, and the diseased state of the mice colon revealed that the pH-sensitive hydrogel is an improved drug delivery system over 5-ASA API commercial preparations as observed in the efficacy and toxicological studies. Xu et al. [75] prepared ibuprofen–*Polygonatum sibiricum* polysaccharide (IBU-PSP) drug delivery system via mechanochemical method. Due to drug delivery and renal protection effect of *Polygonatum sibiricum* polysaccharide (PSP), the solubility of IBU-PSP was increased by a factor of 8.22, and the bioavailability was 2.52 times higher compared with IBU, carrageenin-induced rat paw edema test also increased. Meanwhile, short-term and long-term renal injuries induced by IBU decreased notably. In conclusion, IBU-PSP was a multifunctional drug delivery system with superior anti-inflammatory and renal protection effects.

Curcumin (CUR) loaded micelles self-assembled from Na_2GA were coated with pectin and tannic acid to construct a core-shell solid dispersion (SD-CUR). The assembly mechanism of the core-shell nanoparticle was clarified by molecular dynamics simulation. Improved solubility and *in vitro* release characteristics of SD-CUR were achieved. The PAMPA test confirmed that the permeability of curcumin in SD-CUR was significantly improved compared with pure curcumin. Pharmacokinetic studies showed that the bioavailability increased by a factor of 10 [76]. Figure 15 shows the configuration diagram of CUR loaded micelle system, the number of hydrogen bonds between each component, density distribution and hydrogen bond microstructure.

Ternary solid dispersion of olmesartan medoxomil (OM) was prepared with HP-β-CD and *N*-methyl-*D*-glucamine by mechanochemistry. It showed enhanced solubility and dissolution rate *in vitro*. Pharmacokinetic study demonstrated an improved oral bioavailability *in vivo* [77]. Furthermore, to improve the release property of OM, a ternary solid dispersion consisting of HP-β-CD and hydroxypropyl methylcellulose (HPMC-E5) was prepared by mechanochemical method. The solubility of the solid dispersion could be increased by a factor of 12 as compared with pure OM, and had sustained release performance, affording significantly improved bioavailability of ~ 3-fold in comparison with pure drug [78].

Disodium glycyrrhizinate (Na_2GA), tannic acid (TA) and camptothecin (CPT) were used to prepare the camptothecin solid dispersion (CPT SD). When dissolved in a solution medium, Na_2GA self-assembled to form micelles and CPT was encapsulated in micelles, meanwhile, TA connected with Na_2GA through hydrogen bonds to form a contract shell. The average diameter of the CPT-loaded micelles is 80 nm with the zeta potential of −33 mV, and the polydispersity index is 0.25. *In vitro* experiments confirmed that the drug-loaded micelles exhibited excellent stability and permeability in the intestinal environment [79]. An amphiphilic conjugate of carboxymethyl xylan and nonanoic acid (CX-NA) was synthesised with the molecular weight of 38.35 kDa and hydrophilic-lipophilic balance (HLB) value of 13.5. This conjugate could efficiently encapsulate the model drug of 10-hydroxycamptothecin (HCPT), with an average diameter of 110 nm, zeta potential of −42.88 mV, and drug encapsulation efficiency of 79.8 %. Intestinal *in situ* absorption study further confirmed CX-NA could enhance HPCT to transport across intestinal epithelial cells in colonic tissues. Furthermore, this formulation had improved bioavailability by a factor of 3.4 *in vivo* as compared with free HCPT [80].

Finally, we can describe a good example of complex preparation for plant (grain) protection based on the mechanochemically prepared composite of tebucunazole fungicide, polysaccharide and dry extract of licorice roots. Its application allows a 5–6-fold decrease in the necessary amount of tebuconazole and an increase in grain yield in field [81, 82].

POSSIBLE MECHANISMS OF AN INCREASE IN THE BIOLOGICAL ACTION OF THE OBTAINED SUPRAMOLECULAR DRUG DELIVERY SYSTEMS

The improvement of the bioavailability of drugs from complexes with arabinogalactan is primarily facilitated by an increase in their solubility in wa-

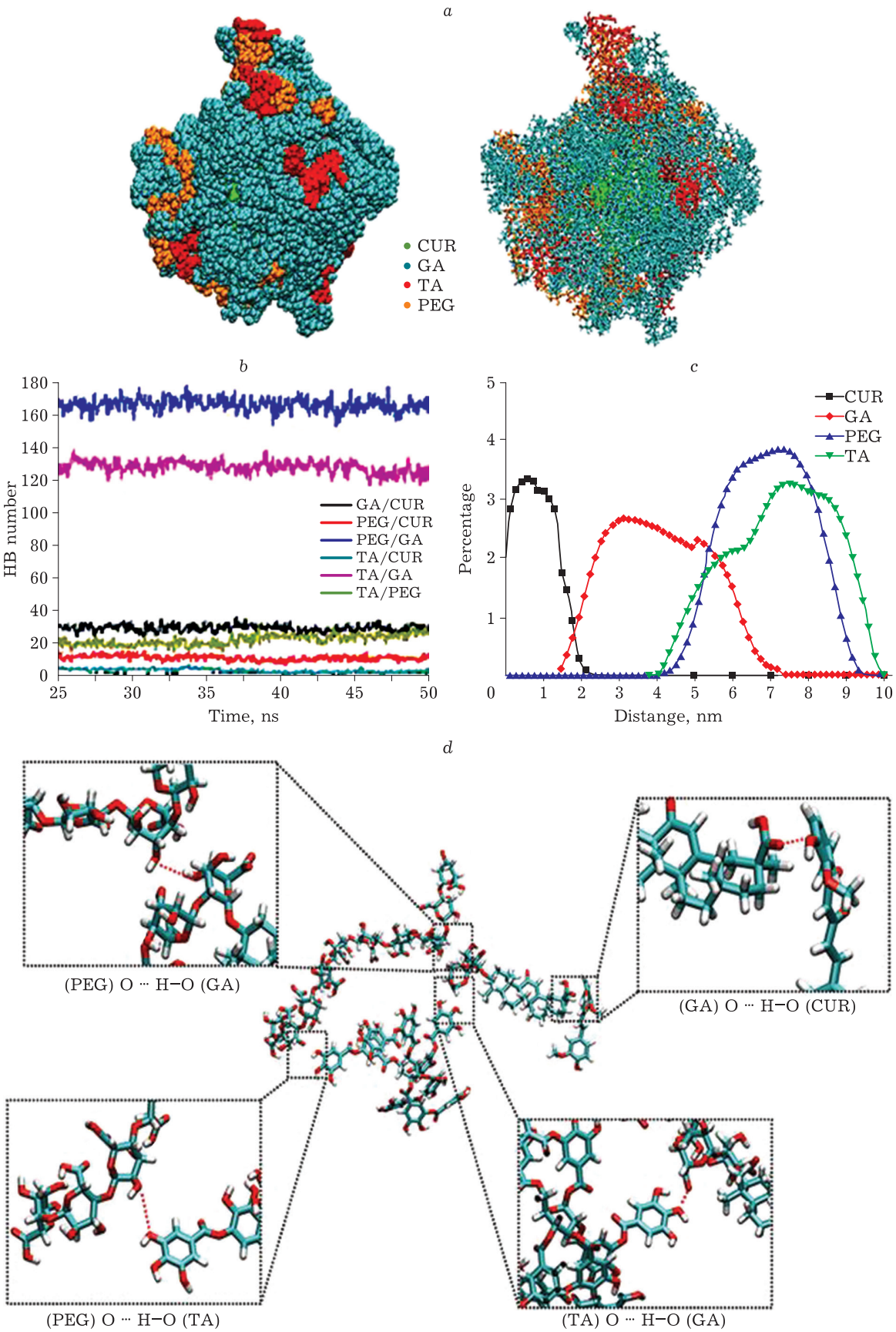

Fig. 15. Configuration diagram of CUR (*a*) loaded micelle system; the number of hydrogen bonds between each component (*b*); density distribution (*c*); hydrogen bond microstructure (*d*).

ter and the adhesion of arabinogalactan molecules to enterocytes. At the same time, it has been shown that macromolecules of arabinogalactan do not penetrate through enterocytes and cannot serve as a means of delivery directly in the bloodstream [62]. The ability of AG to adhere to enterocytes was established *in vitro* on the Caco-2 cell line [83], which is a standard model for evaluating the permeability of a medicinal substance through the gastrointestinal wall *in vivo*. In these experiments, a 2.5 % arabinogalactan solution increased the level of transepithelial electrical resistance by 20 %, reflecting the adhesion of arabinogalactan molecules. This polysaccharide concentration is similar to the applied dose of the complex when administered orally to animals. The guest molecules in the structure of complexes with AG are usually lipophilic substances and, due to the fact that AG creates a high concentration of guest molecules directly on the surface of the intestinal epithelium, their passive diffusion through the lipid bilayer of enterocytes increases. By a similar mechanism, the bioavailability of drug molecules from complexes with cyclodextrins increases.

Also, a more than twofold increase in the absorption of atorvastatin molecules through the cell monolayer was found on the Caco-2 cell line, which may be due to inhibition of P-glycoprotein, since atorvastatin is its substrate [84]. This fact indicates an additional mechanism for increasing bioavailability for molecules from complexes with AG, which are a substrate for P-glycoprotein.

Glycyrrhizic acid can also increase the water solubility of lipophilic molecules and increasing their permeability through the lipid bilayer of enterocytes [4, 64, 84]. However, unlike arabinogalactan, glycyrrhizic acid can integrate into the cell membrane and change its properties, for example, to halve the energy barrier of the lipid bilayer, which, as shown by the example of the complex with nifedipine, significantly increases the permeability of the guest molecule during *in vitro* experiments on an artificial membrane [64].

Table 4 shows the main results of the studies of supramolecular systems.

PROSPECTS FOR FURTHER DEVELOPMENT

In recent years, the list of drugs for which the formation of supramolecular complexes with delivery means has been proven has significantly

TABLE 4

Main results of studies of supramolecular systems

Medicinal/biologically active substances	The main advantages compared to the drugs available on the market	Release form	References
Pesticide preparations for the protection of cereals based on tebuconazole	Reducing the loading of the synthetic fungicide tebuconazole up to 5.5 times, increasing the yield up to 13–20 %	Pesticide preparation for the protection of cereals in the form of suspended powder	[81, 82, 85–87]
Tranquilizers diazepines – sibazone, measepam, azaleptin	Reducing the effective doses of drugs by 2–4 times while maintaining the basic activity	Medicinal product (capsules, granules packed in the form of "sachets")	[59, 88]
Nonsteroidal anti–inflammatory drugs - acetylsalicylic acid, indomethacin, analgin, phenylbutadione, naproxen, ibuprofen	Reducing the effective doses of drugs by 2–4 times while maintaining the basic activity	Medicinal product (capsules, granules packed in the form of "sachets")	[25, 59, 89–92]
Anti-hypertensive and antiarrhythmic – nifedipine, warfarin, amiodarone	Reduction of active doses by 10–100 times	Medicinal product (capsules, granules packed in the form of "sachets")	[93–98]
Polyphenolic and other natural substances of plant origin – quercetin, dihydroquercetin, jenipine, puerarin, curcumin, rutin, carotenoids	An increase in antioxidant and capillary-protective anti-inflammatory action by 3–10 times, antitumor activity	Nutrient product (capsules, granules packed in the form of "sachets")	[99–108]
Anthelmintics – albendazole, fenbendazole, niclosamide, praziquantel	Reduction of active doses of active anthelmintic substances up to 10 times compared to the available drugs	Medicinal and veterinary remedies against the most common human and animal helminthiasis, including opisthorchiasis (capsules, granules packed in the form of "sachets")	[8, 109–118]
Statins – simvastatin, atorvastatin	Increase of lipid-lowering activity and bioavailability up to 3–5 times	Medicinal product (capsules, granules packed in the form of "sachets")	[13, 119, 120]

expanded, and significant progress has been made in understanding the molecular mechanisms of enhancing the biological activity of drugs in such complexes. Thus, the works of the school of Academician G. A. Tolstikov on the design and pharmacological research of systems of "carriers" of medicinal compounds based on plant metabolites, combined with the development of a unique mechanochemical technology for obtaining their supramolecular complexes with API, open up the prospects for creating a wide range of domestic inexpensive medicines for various purposes based on innovative Drug Delivery technologies. Developed by Russian and Chinese scientists, the approach to increasing the effectiveness and safety of medicinal compounds is promising for the creation of anthelmintic drugs of increased efficacy for the treatment of animals and humans [110–112], as well as innovative plant protection products [81, 82, 85–87, 121, 122]. The latter direction is just beginning to develop in the world of agricultural chemistry, preparations using nanoscale delivery means have been called nanopesticides [123, 124]. Studies conducted at the Institute of Solid State Chemistry and Mechanochemistry and the Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences together with the Siberian Federal Research Centre of Agro-BioTechnology of the Russian Academy of Sciences and other institutes of the Russian Academy of Sciences have shown the prospects of this direction in the Russian Federation [48, 59–62]. In particular, using various physicochemical research methods, an increase in the permeability of pesticides in complexes with GA and AG through the shells of corn, barley, rapeseed, wheat grains during pre-sowing seed treatment was demonstrated [48, 59, 60]. At the same time, a significant reduction in plant damage by diseases and pests was achieved. A positive effect of the use of nanopesticides was also obtained during vegetative treatment of plants [63, 64].

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ABBREVIATIONS

5-ASA – 5-amino salicylic acid
AG – arabinogalactan
API – active pharmaceutical ingredient
ArG – arabic gum
AST – astaxanthin
BAS – biologically active substance
CPT – camptothecin
CS – chitosan
CsNIs – celery seed oil/methyl-β-cyclodextrin nanocapsule
CUR – curcumin
CX-NA – carboxymethyl xylan–nonanoic acid
DAI – disease activity index

DDS – Drug Delivery Systems
DNC – 4,4′-dinitrocarbanilide
DOSY – diffusion-ordered spectroscopy
DQ – decoquinate
DSC – differential scanning calorimetry
ESR – electron spin resonance
FDA – Food and Drug Administration
GA – glycyrrhizic acid
HA – hyaluronic acid
HCPT – 10-hydroxycamptothecin
HLB – hydrophilic-lipophilic balance
HPLC – high-performance liquid chromatography
HPMC-E5 – hydroxypropyl methylcellulose
HP-β-CD – hydroxypropyl-β-cyclodextrin
HUA – hyperuricemia
IBU – ibuprofen
IC – inclusion complex
IHN – hexanicotinate
Lg – complexation agent
MD – molecular dynamics
Na_2GA – disodium glycyrrhizinate
NAFLD – non-alcoholic fatty liver disease
NIM – nimesulide
NMR – nuclear magnetic resonance
NOESY – nuclear Overhauser effect spectroscopy
OM – olmesartan medoxomil
PAMPA – the parallel artificial membrane permeability assay
PEG – polyethylene glycol
PM – physical mixture
PRM – protamine
PSD – pharmaceutical solid dispersion
PSP – *Polygonatum sibiricum* polysaccharide
PVP – polyvinylpyrrolidone
PZQ – praziquantel
SA – sodium alginate
SD – solid dispersion
SE-HPLC – size-exclusion high-performance liquid chromatography
SEM – scanning electron microphotography
SIM – simvastatin
TA – tannic acid