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Supramolecular Systems for the Delivery of the Molecules of Medicinal Substances Based on Water-Soluble Plant Metabolites. Physicochemical, Pharmacological Properties and the Features of Mechanochemical Preparation

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Abstract

A brief review summarizes the results of integrated pharmacological and physicochemical studies carried out in the Russian Academy of Sciences, focused on the supramolecular systems for the delivery of the molecules of medicinal substances based on water-soluble plant metabolites – polysaccharides and glycyrrhizic acid, as well as its derivatives. The promising potential of the development of medicines, dietary supplements and plant protection products of increased efficiency and safety is shown. The advantages of the solid-phase mechanochemical technology for obtaining water-soluble compositions of poorly soluble drugs are demonstrated.

Keywords: drug delivery systems, mechanochemistry, polysaccharides, arabinogalactan, glycyrrhizic acid, saponins, vesicular systems, intermolecular complexes, membrane permeability, pharmacokinetic characteristics, bioavailability, toxicity, pharmacological action

INNOVATION DIRECTIONS IN WORLD PHARMACY – DRUG DELIVERY & DRUG DISCOVERY

Development of the technologies in public health, with pharmacy as an integral part, allowed an increase in the average human lifetime by a factor of more than two in the developed countries during the past century and a half. So, most people are doomed to use various medicinal agents in order to maintain and improve their health. Detection of new, previously rare diseases, as well as diseases connected with an increase in lifetime (cardiovascular and oncological) explains the necessity to develop new preparations and improve those currently in existence.

Before 2000-es, the major innovation trend in pharmacy was the creation of new pharmaceutical substances. A special term "Drug Discovery" is used in English to denote this trend. This procedure involves the search and diverse testing of new synthesized or natural chemically modified organic compounds. According to the statistics,

only one compound of about 10 000 starting candidates reaches the stage of industrial production. Tests of preparations may last for many years, 9–12 years as average, while the development cost may be US$ 0.3–2 (0.8 as average) billion [1].

Another direction of innovations is the improvement of the pharmacological properties of the substances that are already used in pharmacy, through the directed delivery to a required site in the organism, organ or cell, as well as the control of the rate, time and site of the action of a medicine in the organism. This direction is called Drug Delivery. As a rule, the duration and cost of developments in this direction are several times less. Nevertheless, this route also allows introducing highly efficient medicines [2–4].

For the above-described economic reasons, the specific weight of developments in the area of Drug Delivery becomes dominating at present. For instance, the world sales volume of the medicines manufactured according to the Drug Delivery technology in 2017 is estimated to exceed US$ 500 billion [5], with the predicted annual increase by ~7 %, while the market of "new molecules" – Drug Discovery – accounts for about US$ 40 billion [6]. It should be noted that the accelerated growth of developments in Drug Delivery is especially preferable for the countries possessing an insufficient level of the production of their own drugs, but tending to accelerated progress in this area. It is this group of countries to which Russia belongs; the fraction of preparations manufactured in Russia occupies not more than 1/3 of the market in value terms, while with respect to the number of packs sold it is up to 2/3. In fact, Russian pharmacological industry manufactures mostly outdated cheap preparations. The demand for efficient and safe pharmaceuticals is satisfied by the import of more expensive medicines.

SUPRAMOLECULAR DELIVERY SYSTEMS FOR ORAL PHARMACEUTICAL FORMS. ADVANTAGE OF PLANT METABOLITES

Solid dosage forms (tablets, capsules, drops etc.) are most popular for use in the so-called developed countries: their sales volume reaches ~85 % of the pharmaceutical market [7]. However, not less than 40 % of these preparations possess substantial disadvantages – they are classified as practically insoluble. This causes the necessity to use increased doses of medicines, worsens the drug efficiency due to non-optimal pharmacokinetic parameters, and often leads to unfavourable side toxic effects [8]. Studies connected with the development of innovative domestic preparations within the Drug Delivery technology were launched at the Novosibirsk Institute of Organic Chemistry named after N. N. Vorozhtsov (NIOCh SB RAS) under the supervision of Academician Tolstikov G. A. in collaboration with other institutes of the Siberian Branch of the Russian Academy of Sciences. It was demonstrated in numerous experiments with animals that the formation of the complexes between the molecules of pharmaceutical substances (PS) and specially selected plant glycosides and polysaccharides allows a substantial (10–150 times) decrease in the therapeutically active dose, a decrease (down to complete disappearance in some cases) in harmful side effects and, in some cases, enhancement of non-typical (so-called pleiotropic) properties of preparations [9–11]. It was shown that so essential and favourable changes in pharmacological characteristics occur due to the formation of guest-host supramolecular complexes in which PS molecules are guests, while the hosts are polysaccharide macromolecules, glycoside micelles and so on. The pharmacological effect of these structures may be achieved due to some factors; the major ones are an increase in solubility, membrane permeability, bioavailability, a decrease in pre-systemic metabolism by the enzymes of the gastrointestinal tract etc. So, due to the use of the Drug Delivery approach, the delivery of medicine molecules to the active centres of the corresponding systems of the organism becomes simplified.

According to our experience, the most efficient hosts among the studied substances are water-soluble substances of plant origin – glycyrrhizic acid (Fig. 1) and polysaccharide arabinogalactan.

Glycyrrhizic acid (GA) is a triterpenic glycoside from the extract of licorice roots. It exhibits a broad range of biological activity and is used in medicine for treatment and prophylactics of various diseases [12, 13]. Chemically, the molecule of glycyrrhizic acid possesses lipophilic-hydrophilic properties characteristic of plant saponins; it forms associates in aqueous solutions – dimers and micelles into which the molecules of medicines may get included [14–20]. In turn, this opens broad opportunities for the use of GA as a tool for drug delivery [10, 12, 21]. There are reasons to suppose that GA may be used for targeted delivery of medical preparations into liver tissues [22, 23]. In particular, it was reported that the conjugates of GA are efficient for the targeted deliv-

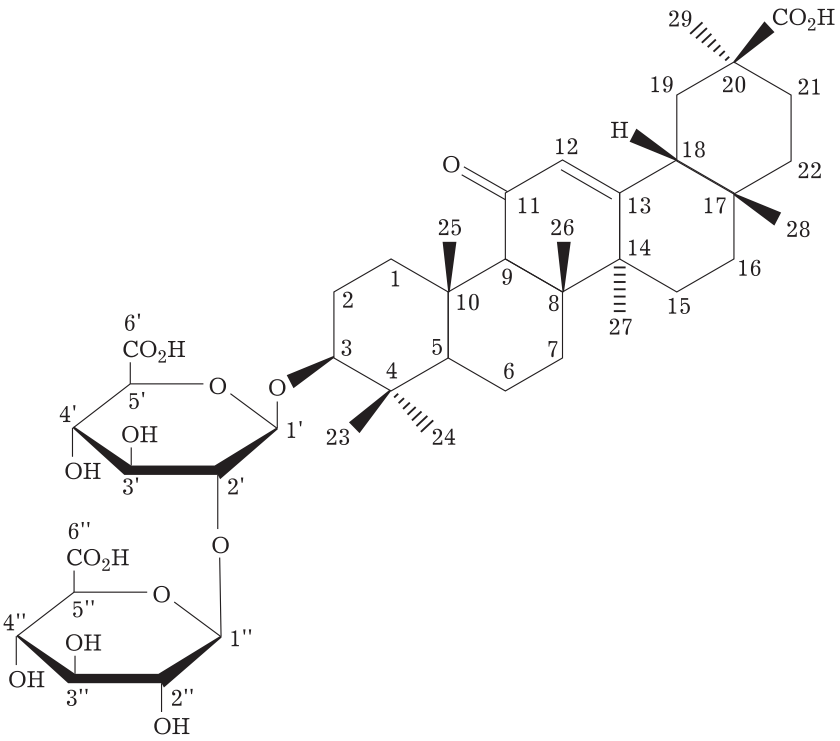

Fig. 1. Structure of glycyrrhizic acid.

ery of doxorubicine (antibiotic of anthracycline series exhibiting anti-tumour activity) into liver cells [23]. Similar effects were noticed also for the formation of GA complexes with pharmaceutical preparations of other classes [24–26].

Another promising compound is water-soluble polysaccharide arabinogalactan (AG) extracted from the wood of Siberian larch *(Larix sibirica)* and Gmelin larch *(Larix gmelinii)* [27]. AG content is up to 15 % of the dry wood mass. It is necessary to stress that both larch species are the major constituents of woodlands in Gorniy Altai and East Siberia. AG is isolated and purified according to the technology developed at the Irkutsk Institute of Organic Chemistry named after A. E. Favorsky, Siberian Branch of the Russian Academy of Sciences. The wastes from felling, sawmilling, pulp and paper industry can be used as the raw material. So, AG due to its availability has no competitors among natural and biosynthetic polysaccharides. At present, AG substance is manufactured at some plants in Russia and used as a biologically active additive (BAA) to food. AG macromolecules from larch wood have a branched structure. The main chain of the macromolecule is composed of galactose links connected through β-(1→3)-glycoside bonds, while the side chains bound to the main chain by β-(1→6)-glycoside bonds are composed of galactose and arabinose links, from single arabinose links, as well as uronic acids, mainly glucuronic [27]. These structural features promote the formation of strong complexes with PS. The ability of GA and AG to form supramolecular complexes is surprising not only because of the broad range of PS involved but also because of the inevitable appearance of above-described advantages in resulting preparations [17]. However, for the practical application of AG and GA in pharmaceutics, it is necessary to understand the molecular mechanisms of the enhancement of therapeutic activity of medicines in the complexes with these delivery means. It is this problem that has been the subject of investigations carried out at the Institute of Solid State Chemistry and Mechanochemistry (ISSCM), NIOCh and Institute of Chemical Kinetics and Combustion (ICKC) of the Siberian Branch of the Russian Academy of Sciences.

ADVANTAGES OF THE MECHANOCHEMICAL ROUTE OF OBTAINING SUPRAMOLECULAR COMPLEXES

One of the advantages of the developments of new drug delivery systems at the Novosibirsk Scientific Centre is the application of solid-phase mechanochemical technology of obtaining supra-

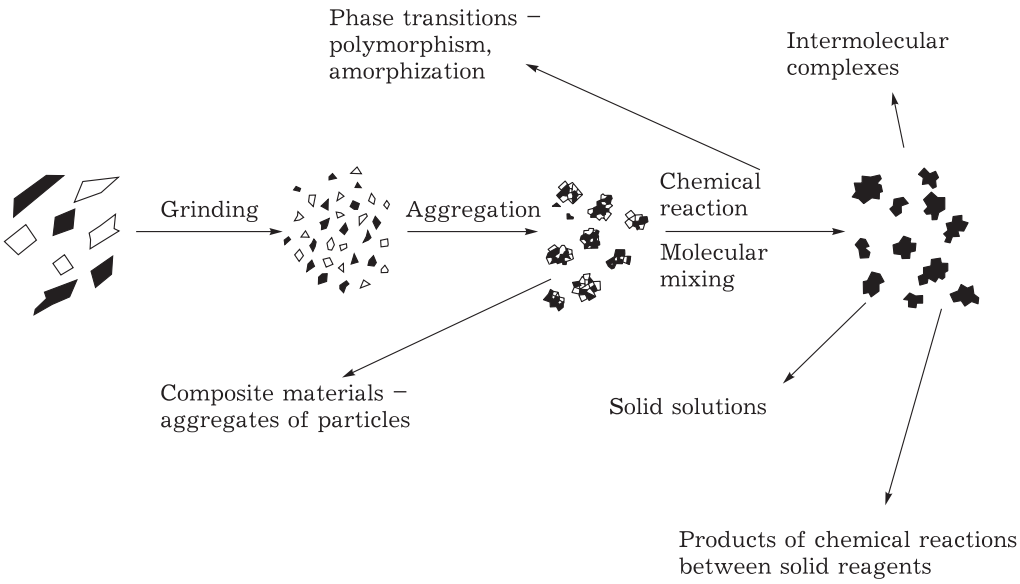

Fig. 2. Scheme of mechanochemical transformations of the mixture of organic compounds.

molecular complexes, which are inclusion complexes of poorly soluble pharmaceutical substances with delivery means. It may be stated that Russian scientists keep the leading positions in this area. Large-scale studies in this direction started in the 60-es of the past century; in the Siberian Branch of the Russian Academy of Sciences the most intense studies in this area were carried out in the scientific school supervised by Academician Boldyrev V. V. Though PS exhibit their pharmacological action in solution, the properties of a solution are strongly determined by the composition and structure of initial solid species, and solid phases are the direct object for investigation in solid state chemistry.

During the recent decade, the promising nature of the mechanochemical technology for obtaining improved drug delivery systems was substantiated in the joint works carried out by the researchers from the ISSCM, NIOCh, ICKC and other institutes of the Siberian Branch and other branches of the Russian Academy of Sciences in collaboration [17, 28, 29]. Mechanochemistry of solid substances investigates the transformations of these substances under high pressure and deformation. There are many designs of the devices in which the conditions for mechanochemical transformations are created. The most popular devices are mills for dry milling of solids. However, the treatment is not only reduced to the comminution of the materials. The transformations of solids in mechanochemistry are diverse (Fig. 2).

One can see that comminution is only the first stage, then the crushed particles are gathered to form aggregates; continued mechanical activation leads to a kind of molecular mixing of the solids. Depending on the nature of substances, chemical reactions may proceed, or the solid phases may be formed, in which the molecules enter various interactions. Those who are acquainted with traditional chemistry may think it is surprising that there is the possibility of chemical reactions between solids without the participation of liquid phases. It is not less astonishing that not very high energy losses may result in obtaining a composite material in which each powder particle is an aggregate of ultrafine particles of the solid reagents. Then, under thermal action or hydration, a chemical reaction leading to the formation of target products proceeds rapidly. All these possibilities were demonstrated by us in the early 1990-es [30, 31].

MECHANISMS OF THE ENHANCEMENT OF THE PHARMACOLOGICAL ACTIVITY OF MEDICINES IN THE INCLUSION COMPLEXES WITH DELIVERY MEANS

Diverse approaches are used in the direction of the development of innovative drugs according to the Drug Delivery principle. At present, the most popular approach is perhaps the targeted delivery of the drugs to the site of pathological processes in an organism or to sensitive receptors. For this purpose, the molecules of PS are attached to carrier particles which carry out the

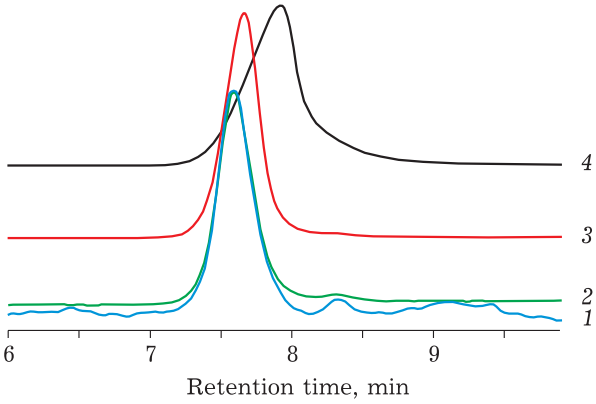

Fig. 3. Gel-filtration chromatograms of the solutions of GA with different concentrations, %: 0.001 (*1*), 0.01 (*2*), 0.1 (*3*), 0.5 (*4*).

targeted delivery. Not less relevant are the methods of PS solubility and dissolution rate enhancement. Solubility plays a substantial part in the action of drugs, first of those intended for oral intake, because the maximal rate of the passive transport of a preparation through biological membranes is the main route of the absorption of PS – depends on membrane permeability and on concentration. It should be stressed that the formation of water-soluble supramolecular complexes, as a rule, is also accompanied by an increase in PS solubility in water. Moreover, the degree of an increase in solubility is the evidence of the strength of complexing, and it is convenient to use this parameter as a measure of the stability of the formed supramolecular systems of guest-host type [32].

It turns out that the mechanochemical technology provides the most efficient route to obtain the solid compositions of PS forming the entire range of guest-host type delivery systems during dissolution. In comparison with the known traditional liquid-phase synthesis technologies, the mechanochemical technology allows one to combine the substances independently of their solubility, to make stronger guest-host systems, and to avoid undesirable side chemical reactions. Depending on the lipophilic properties of guest molecules and the strength of the resulting supramolecular systems of the guest-host type, we observed an increase in solubility up to 10^3 times in our experiments. It should be noted that the strength of complexes obtained mechanochemically is 1–2 orders of magnitude higher as a rule than that for the complexes obtained by mixing the components in solution.

According to the results of X-ray phase and thermal analysis of the resulting compositions, untreated mixtures always contain the reflections characteristic of the crystal phases of PS (in the diffraction patterns) and the phase transition of melting (in thermograms) which disappear or decrease substantially after mechanical treatment in mills. This is the evidence that partial or complete loss of crystallinity of the studied PS is characteristic of the mechanically treated mixture. This is accompanied by disordering of the solid phase of PS, molecular dispersing of the PS into the excess of the solid-phase complex-forming agent with the formation of solid solutions or intermolecular complexes. In the latter case, the change in solubility points to the formation of stronger complexes in the solid phase than from the aqueous solutions of the compositions under investigation. The hydrate shell of hydrophilic supports – AG and GA – is likely to hinder the formation of guest-host systems.

In addition, during the recent years, we carried out a series of the physicochemical studies of the properties of resulting compositions in solutions, which allowed us to establish the molecular mechanisms of the enhancement of bioavailability of many PS in the complexes of inclusion with delivery means – GA and AG. In the case when the compositions based on GA and AG are dissolved, the nature of supramolecular formations changes. It was established that GA, after dissolution in the aqueous medium, forms various self-associates – from dimers in the case of low concentration to micelles in the case of concentrations higher than the critical concentration of micelle formation [14–19]. For instance, it was demonstrated by means of gel chromatography that the micelles of GA have a mass of 46–67 kDa and are composed of 50–80 molecules of this acid [16, 17]. Examples of gel chromatograms of GA solution are shown in Fig. 3.

It was demonstrated by means of NMR relaxation that the dissolution of mechanochemically synthesized compositions is accompanied by the inclusion of PS molecules in GA micelles [33–37]. Due to the high sensitivity of the time of spin-spin nuclear relaxation to the rotational mobility of molecules, NMR relaxation has won wide application in the studies of intermolecular interactions in solutions, in particular, to confirm the formation of inclusion complexes of PS and to investigate their interaction with cell membranes [37–43]. Thus, the times of proton relaxation decrease by a factor of several ten as a result of the formation of inclusion complexes with AG and GA. Figure 4 shows an example of the kinetics of

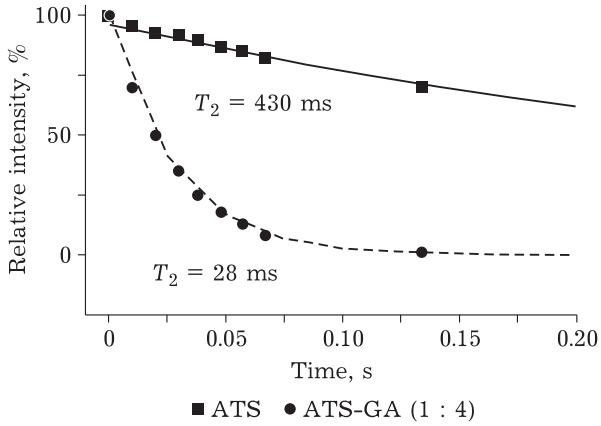

Fig. 4. Dependence of the intensity of NMR signal from the aromatic protons of atorvastatin (ATS, concentration 2 mmol/L) on time in a 40 % water-methanol solution in the absence (1) or in the presence (2) of GA (ATS-GA = 1 : 4) at a temperature of 30 °C. Points – experiment, continuous lines – calculation.

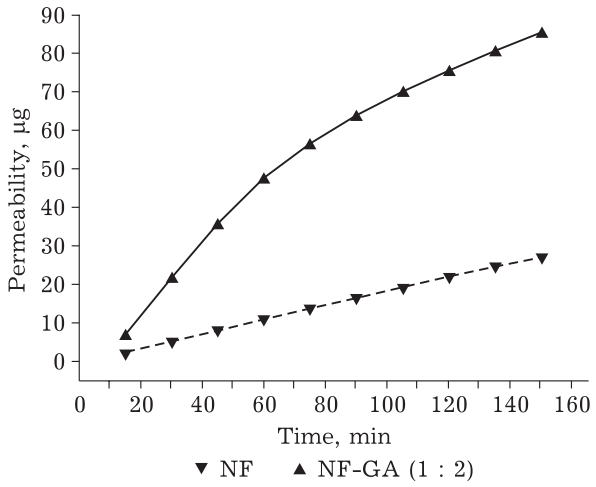

Fig. 5. PAMPA experiment: the kinetics of the transport of NF molecules through a model membrane in the free form and in complex with GA (NF-GA = 1 : 2). Pure NF was used in the saturated solution in water at 37 °C. Concentration of complex: 5 mg/mL.

a decay of NMR signal in the relaxation experiment for the aromatic protons of atorvastatin (ATS) in the absence and in the presence of GA. It should be stressed that a feature of GA is its ability to form associates and complexes with PS molecules not only in water but also in organic solvents [12].

Analysis of the experimental data on the measurement of the times of proton relaxation during complex formation allowed us to reveal substantial advantages of the mechanochemical technology of obtaining inclusion complexes. It was shown that molecular dispersion of medicines in the polymeric matrix of AG is conserved during the dissolution, and more stable complexes are formed than those formed after the dissolution of a mixture of substances without their preliminary mechanical activation. The dissolution of non-activated physical mixture of poorly soluble pharmaceutical compounds with delivery means is very often accompanied by rapid aggregation of drug molecules and their precipitation. Mechanical activation of the mixture causes a substantial decrease in the contribution from self-association [44, 45].

It was shown that the delivery means (AG and GA) are able not only to enhance the solubility of included compounds but also to increase their permeability through membranes. It was established that GA is able to increase the permeability of the membranes of erythrocytes and the cells of myeloid leucosis for model molecules through the insertion into the lipid bilayer of the membrane [38, 39]. The ability of GA to penetrate inside the lipid bilayer and interact with the lipid membrane was established by means of NMR and molecular dynamics. GA molecules may affect the molecular mobility of membrane components (lipids and cholesterol) having a membrane-mediating effect on the proteins bound to the membrane, and affecting their activity [40–43]. This may partially reveal the effect of GA on the therapeutic properties of pharmaceutical compounds in supramolecular complexes.

In the case of complexes with AG, a concentrational mechanism of an increase in oral absorption is likely to take place [46]. This mechanism is based on an increase in the local concentration of guest molecules, in particular, due to probable adhesion of GA molecules to the cells of the intestinal epithelium.

To model the absorption of preparations in the gastrointestinal tract *in vitro*, high efficiency was demonstrated by the method of transmembrane transport investigation using artificial membranes, so-called Parallel Artificial Membrane Permeability Assay – PAMPA. This method was initially developed for screening the membrane permeability of individual molecules of pharmaceutical compounds [47], however, at present it is successfully used also to study the inclusion complexes of PS molecules [26, 48]. As an example, Figure 5 shows the kinetics of the transport of nifedipine molecules through a model membrane

in the free form and in complex with GA (nifedipine-GA = 1 : 2).

PHARMACOLOGICAL PROPERTIES OF COMPOSITIONS WITH DELIVERY MEANS

Examples allowing evaluation of the potential of our approaches are described below. Antihypertensive preparation Nifedipine, which had been used successfully for several decades to treat hypertonia, was forced out by more expensive analogues. However, with the appearance of new pharmaceutical dosage forms of nifedipine, the interest of doctors to this cheap preparation revived. The form of nifedipine with GA proposed by us is to occupy a special place among cardiovascular preparations [35, 49]. What is the feature of our preparation? It exhibits the necessary antihypertensive activity (with intravenous introduction) with nifedipine dose decreased by a factor of 10. The combination with GA causes a powerful enhancement of the secondary effect of nifedipine – its antiarrhythmic action. Its solubility increases several times, therefore, so does the possibility to use it in intravenous injections for acute care. The application of the preparation developed by us will promote a substantial reduction of the risk of progressive stenocardia and other cardiovascular complications, and prevent the development of hepatic and renal insufficiency. Thus, the transformation of nifedipine in this form makes it a polyfunctional preparation. The number of the preparations of this kind at the drug market is not high.

The preparations called statins are efficient means to decrease low-density lipoproteins and total cholesterol. The breadth of their application for the therapy of atherosclerosis may be illustrated by the sales at the drug market. For instance, the sales volume of the preparations based on synthetic statin – atorvastatin – exceeded 10 milliard US dollars per year. In Russia, a one-year course of Liprimar preparation costs about 20 thousand roubles. Investigations carried out by the NIOCh SB RAS in collaboration with the Institute of Therapy, SB RAMS allowed us to establish that the supramolecular complexes of statins with GA allow a 3–5 times decrease in the therapeutic dose of the expensive PS and substantial reduction of hazardous side effects [24, 44, 50, 51].

Other examples are not less convincing [25, 26, 45, 52–54]. Widely used nonsteroid anti-inflammatory medicines aspirin, orthofen, indomethacin, analgin and so on have a substantial disadvantage – destructive changes in the mucous coat of stomach. It was shown that the supramolecular complexes of these medicines with GA and AG provide efficient action in doses decreased substantially (by a factor of 2–20). An especially important feature of the preparations is a sharp decrease in toxicity and the degree of destructive damage of mucous coat of stomach. In addition, the protectability of liver and kidneys. Similar changes in activity – a multiple (up

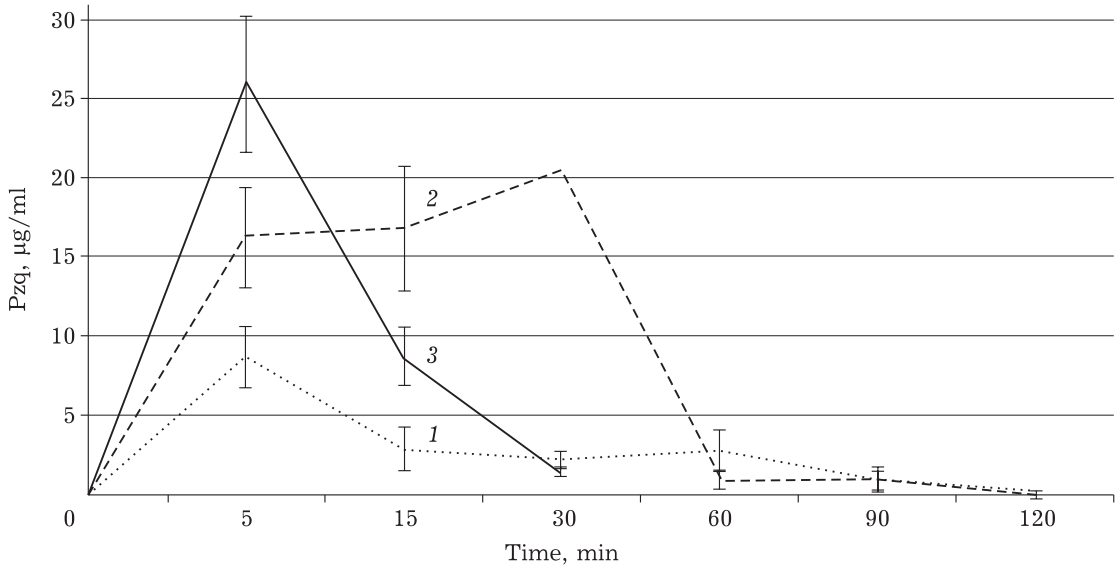

Fig. 6. Comparative pharmacokinetics of oraziquantel (Pzq) content in the blood of laboratory animals (mice) after the intake of different forms of preparations with the equivalent Pzq doses: *1* – praziquantel substance; *2* – composition Pzq–Na_2GA [25]; *3* – composition Pzq–AG.

to 20 times) decrease in the effective dose – are observed for the combinations of tranquilizer drugs sibazon, mezapam, neuroleptic drug azaleptin, antiarrhythmic drug amiodarone, antioxidant dihydroquercetin and others with AG.

A very promising direction of our studies is the development of antihelminthic preparations for medicine and agriculture on the basis of the widely used drugs praziquantel, albendazole, fenbendazole and niclosamide. Complex-forming agents were GA and its salts (in particular disodium salt of glycyrrhizic acid – Na_2GA), AG and hydroxyethylstarch. In all cases, both with laboratory animals and with agricultural ones, the possibility of a multiple (3 to 11 times) decrease in the effective doses of preparations was demonstrated, along with a decrease in the toxicity of the drugs [25, 37, 54, 55]. One of the examples illustrating the biological mechanism of the enhancement of the efficiency of one of the most popular PS – praziquantel (PZQ) – is its pharmacokinetics in laboratory animals as shown in Fig. 6.

As a total, we studied several ten widely used PS, and in the majority of cases we succeeded in achieving the advantages discussed above. The major results obtained in these studies are summarized in Table 1.

The main result of the studies was the development of the preparations as candidates for clinical studies: glycidipine – hypotensive and antiarrhythmic medicine, simvaglyzin – the first

TABLE 1

Major results of the investigation of supramolecular systems based on plant metabolites with the inclusion of pharmaceutical and biologically active substances

Pharmaceutical/ biologically active substances	Complexing plant metabolites	Supramolecular systems of delivery/ an increase in solubility	Results of pharmacological tests	References
Fungicidal preparations for cereals, based on tebuconazole	Arabinogalactan, salts of glycyrrhizic acid, dry extract of licorice root	Complexing, inclusion in micelles / up to 10 times	An increase in fungicidal activity, growth stimulation, a decrease in the effective doses of tebuconazole by a factor of 2–5, an increase in crop capacity up to 10 %	[48, 61–67]
Tranquilizers diazepins — sibazon, mezapam, azaleptin	Arabinogalactan, glycyrrhizic acid, pectin	Complexing, inclusion in micelles / up to 50 times	An increase in bioavailability, a decrease in effective dose by a factor of up to 20	[32, 68]
Nonsteroidal anti-inflammatory preparations – acetylsalicylic acid, indomethacin, analgin, phenyl butadion, naproxen, ibuprofen	Arabinogalactan, glycyrrhizic acid, pectin	Complexing, inclusion in micelles / up to 30 times	An increase in bioavailability, an increase in basic pharmacological activity, a decrease in effective doses	[32, 45, 69–73]
Antihypertensive and antiarrhythmic – nifedipine, warfarin, amiodarone	Arabinogalactan, glycyrrhizic acid	Complexing, inclusion in micelles / up to 30 times	A decrease in effective doses by a factor of 10–100	[49, 53, 74–77]
Polyphenol and other natural substances of plant origin – quercetin, dihydroquercetin, genipin, puerarin, curcumin, rutin, carotenoids	Arabinogalactan, glycyrrhizic acid, salts of glycyrrhizic acid	Complexing, inclusion in micelles / up to 1000 times	An increase in the antioxidant and capillary-protecting action by a factor of 3—10, anti-tumour activity, an increase in bioavailability by a factor of up to 20	[26, 52, 78–85]
Antihelminthics – albendazole, fenbendazole, niclosamide, prasiquantel	Arabinogalactan, glycyrrhizic acid and its salts, hydroxyethyl starch	Complexing, inclusion in micelles / up to 500 times	An increase in antihelminthic activity, bioavailability, a decrease in toxicity and effective doses by a factor of up to 10	[25, 37, 54, 56-58, 86–99]
Statins – simvastatin, atorvastatin	Arabinogalactan, salts of glycyrrhyzic acid	Complexing, inclusion in micelles / up to 300 times	An increase in hypolipidemic activity and bioavailability 3–5 times	[66–68]

hypocholesterolemic agent in Russia, flyoglyzine – low-dose antidepressant etc.

OUTLOOKS OF FURTHER DEVELOPMENT

The list of PS for which the formation of supramolecular complexes with delivery means was proved is getting much broader during the recent years; substantial progress has been achieved in the understanding of the molecular mechanisms of the enhancement of biological activity of medicines in these complexes. So, the works carried out by the scientific school of Academician G. A. Tolstikov on the design and pharmacological studies of the systems of carriers of medicinal agents based on plant metabolites in combination with the development of the unique mechanochemical technology of obtaining their supramolecular complexes with PS open the outlooks for the creation of a wide range of domestic cheap pharmaceuticals for various purposes on the basis of the innovative Drug Delivery technologies.

The approach developed by us for an increase in the efficiency and safety of pharmaceutical compounds was also successfully used in collaboration with other research institutes (ICG SB RAS, VNIIP named after K. P. Skryabin, INEOS RAS) for the development of new antihelminthic preparations with increased efficiency to treat humans and animals [55–58], as well as innovative means of plant protection [48, 59–65]. The latter direction is only starting its development in the world agricultural chemistry, the preparations involving nanosized delivery means are called nanopesticides [100, 101]. Investigations carried out at the ISSCM SB RAS and ICKC SB RAS together with SFSCA RAS and other institutes of RAS demonstrated the potential of this direction of the development of the agroindustrial complex of the RF [48, 59–62]. In particular, with the help of various physicochemical methods, we demonstrated an increase in the permeability of pesticides in complexes with GA and AG through the grain shells of corn, barley, rape, wheat during the presowing treatment of seeds [48, 59, 60]. Substantially lower affection of plants by diseases and pests was achieved. A positive effect of the application of nanopesticides was obtained also from the vegetative treatment of plants [63–65].

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