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Intermolecular interactions of apple pectin modified by pharmacophores with iodine and antimicrobial activity of iodine-containing pectin materials

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ABSTRACT

New complex compounds based on apple pectin and pharmacologically active organic acids (nicotinic, salicylic, 5-aminosalicylic and anthranilic acids) were synthesized. The obtained complexes were characterized by a number of physicochemical research methods (UV, IR, and ^{13}C NMR spectroscopy, electron microscopy, viscosimetry, polarimetry, and elemental analysis). Based on pharmacophore-containing pectins, stable iodine-containing films were obtained. The effect of the structure of a polysaccharide-modifying drug compound on the properties of iodine-containing polymeric materials was shown: iodine content, time of release of iodine from the film, diffusion and surface characteristics. The formation of a new set of properties in the production of iodine-containing films based on pharmacophore-containing pectins provides an increase in antimicrobial activity by 1.3-1.5 times in comparison with the initial polymer matrices.

Keywords: *pectin; medicinal compounds; iodine; complexation; biological activity.*

1. INTRODUCTION

The use of biopolymers to create long-acting drugs that combine the drug effectiveness with address delivery to the target is an actual tendency of bioorganic chemistry. Polysaccharides complexes with biologically active compounds of organic and inorganic nature are among the most interesting [1-13]. A natural polysaccharide – pectin (PC) has proved to be a good polymer matrix, which not only contains functional groups providing effective complexation, but also has a variety of biological activity and is easily biodegradable [14-18]. Regarding all this, pectin can be considered as a promising basis for the creation of new drugs with different spectrum of action.

The functional properties of the materials obtained by immobilization of the drug substance (DS) on the polymer matrix depend both on the biological action of the low molecular weight component and on the mutual influence of the polymer matrix and pharmacologically active substance on each other's properties [19, 20]. Therefore, the understanding of the nature and strength of drugs binding with biopolymer will allow determining the prospects of using the obtained complex materials for medicine and pharmacology, as well as the methodology for the introduction of inorganic components (for example, iodine) to impart antiseptic and antibacterial properties to new biomaterials. Modern medicine, with a wide arsenal of antibacterial agents, faced with the problem of the resistance development of microorganisms to antibiotics. It seems attractive to introduce iodine into the modified pectin matrix, for there is no fact of habituation for any of the known microorganisms to iodine [21]. However, iodine has an irritating effect on the tissue and is toxic in large quantities, which limits its use. The reduction of toxicity and uniform release of iodine is facilitated by its immobilization on a polymer matrix, additional modification of which by organic compounds can contribute to the production of iodine-containing drugs that are resistant to long-term storage and have a synergistic therapeutic effect [22-26]. This article discusses the results of a study of the apple pectin interaction with organic and inorganic biologically active compounds and the conditions for obtaining new stable iodine-containing materials with controlled dynamics of iodine release. Pharmacologically important compounds: nicotine (NA), salicylic (SA), 5-aminosalicylic (5-ASA) and anthranilic (AA) acids were selected as low molecular weight organic components [27].

2. MATERIALS AND METHODS

2.1.Materials.

Apple pectin of Unipectine XPP240 trademark with molecular weight 26000 Da and degree of esterification 66% was used. All medicinal compounds: NA, SA, 5-ASA, AA, mark "c.f.a.", were used without further purification. Iodine metal, mark "c.", twice sublimed was used in experiments.

2.2.Physico-chemical methods.

IR spectra were recorded on Shimadzu IR-Prestige-21 spectrophotometer (700-3600 cm^{-1}, vaseline oil). ^{13}C NMR spectra were recorded on the Bruker Avance III 500 MHz spectrometer (solvent D_2O, concentration 10 $mmol \cdot l^{-1}$). The characteristic viscosity of aqueous solutions of the samples was measured at 25±0.1 °C in a capillary Ubbelode viscometer with a hanging level. The samples surface properties were studied using an electron microscope AxioLab Pol. The specific rotation of aqueous solutions of compounds (C=0.1 g/100 ml) was measured using a Perkin-Elmer polarimeter (model 141). UV spectra of solutions were recorded in quartz cuvettes on a UV−VIS

SPECORD M−40 spectrophotometer in the 220-900 nm region. The composition and stability constants of the formed compounds in the interaction of PC with pharmacophores and in the interaction of PC and/or pharmacophore-containing pectin (PCP) with iodine were determined by spectrophotometric methods of isomolar series and molar ratios [28]. The total concentration of the PC and DS in isomolar series has been a constant of $1\cdot10^{-5}$mol/l for PC+DS systems. Molar ratio of [PC]/[DS] was varied from 50/1 to 1/20. The PC concentration was changed from $0.25\cdot10^{-5}$ and to $1\cdot10^{-3}$mol/l in the series of solutions with a constant drug concentration of $1\cdot10^{-5}$mol/l. For the PC+I_2 and/or PCP+I_2 systems, the total concentration of PC and/or PCP and iodine in the isomolar series was constant $1\cdot10^{-4}$mol/l. The molar ratios [PC]/[I_2] and/or [PCP]/[I_2] varied from 50/1 to 1/20. In a series of solutions with constant iodine concentration of $1\cdot10^{-4}$mol/l, concentration of PC and/or PCP has changed from $0.25\cdot10^{-4}$ to $1\cdot10^{-2}$mol/l. Ionic strength of solutions was maintained constant, equal to 0.1 mol/l (NaCl, "ch. c.").

2.3.Preparation of pharmacophore-containing pectins

1 g of polysaccharide was dissolved in 20 ml of water with pH 7-7.1. 0.70 g of DS were dissolved in 20 ml of water,solution pH being adjusted to 7-7.1 with 0.1 M NaOH solution. The DS solution at 25 °C was added to the polysaccharide solution under intensive stirring. The reaction was carried out for 4 hours. At the end of the reaction the product was isolated by precipitation with ethyl alcohol, once more precipitated with alcohol, the precipitate was separated and washed three times with alcohol, then with diethyl ether and dried under vacuum at a temperature of 25 °C.

2.4.Preparation of PCP-based films.

Film materials based on PCP and PC were formed from 2% aqueous solutions of compounds by casting on a glass substrate, followed by evaporation of the solvent in vacuum over phosphorus pentoxide. Further, the films were vacuum-dried at 25 °C to a residual humidity of 5-7%. The film thickness in all experiments was maintained constant and equal to 0.1 mm.

2.5.Preparation of PCP iodine-containing films.

Doping of PC or PCP films was carried out at room temperature as follows: weighted samples in glass containers were placed in a desiccator purged with argon, wherein another containera metal iodine was placed. The degree of iodine saturation was assessed by maintaining a constant weight of the samples at exposure for three days. The total iodine content in the samples was determined gravimetrically. The total content of molecular iodine was determined by iodometric titration [29].

2.6.Biological activity.

Antimicrobial activity of the complexes was determined by the disc-diffusion method. To determine the sensitivity, a nutrient medium prepared from meat-peptone broth with agar-agar addition was used. Meat-peptone agar 4 mm thick was poured in sterile Petri dishes and pure cultures of purulent infection pathogens *(Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli)* were seeded by the "solid lawn" method. No later than 5 minutes after inoculation, the studied compounds were applied to the surface of the nutrient medium. After that Petri dishes were incubated at 37 °C for 24 hoursin a thermostat. After incubation, the size of the growth delay zones of microbial cultures at the application places of the studied systems was estimated.

3. RESULTS

3.1. Physico-chemical characteristics of PCP.

PC interaction with DS was studied by UV, IR and NMR ^{13}C spectroscopy, electron microscopy, viscosimetry, polarimetry and elemental analysis. The data obtained show that the apple pectin forms 1:1 complexes with selected organic substances (i.e. 1 drug molecules per 1 pectin monomer unit).This is confirmed by elemental analysis (Table 1) and spectrophotometric studies using the method of isomolar series and molar ratios(Fig. 1, 2).

The values of PC complexes stability with investigated drugs (Table 2) show that the complexation effectiveness depends significantly on the structure of the pharmacophore. According to the results, the stability of the complexes (β_k) increases as follows: PC-NA>PC-5ASA>PC-AA>PC-SA.

As expected, nitrogen-containing pharmacophores exhibit a greater affinity for biopolymer in comparison with salicylic acid. This is quite consistent with the tendency of the heteroatom within the second period to redistribute the electron density to the acceptor (N>O>F).

Formation of PC complexes with pharmacophores is also confirmed by IR and ^{13}C NMR spectroscopy. The shifts of absorption maxima of ν(C=O), ν(OH), ν(C-O, C-C) PC groups to the low frequency region are observed in the IR spectra (Table 2, Fig. 3). The most significant displacements are recorded for PC ν(C=O) group.

The results of ^{13}C NMR spectroscopy are presented in Tables 3, 4. It can be seen that all DS carbon nuclei signals are shifted towards the weak field after complexation. The most significant shifts of ^{13}C nuclei signals are observed for carbon atoms directly connected to the amino group (in case of AA and 5ASA), to heteroatom (in case of NA), and to hydroxyl group (in case of SA).

According to the spectral data, the following structures of pectin complexes with pharmacophores can be suggested (Fig. 4).

PCP microstructure analysis showed that the pharmacophores with ordered structure lead to a more ordered structure of PCP (e.g. PC-NA). Amino-containing drugs do not have a structure-organizing effect on the polymer matrix (Fig. 5). Thus, the pharmacophore heteroatom contributes to the structuring polymer complex, which may lead to sustainability. It was found that the complexation of PC with DS increases the characteristic viscosity for the PC-NA system, containing heteroatom in the ring, and a significant drop in this parameter for the remaining aromatic acids compared to the unmodified biopolymer (Table 2). The viscosity increase for PC-NA is associated with the structuring of the macromolecule, the increase in its rigidity, and as a consequence, the unfolding of the polymer chains. The decrease in viscosity for the remaining samples indicates the compression of the macromolecular ball, due to the aromatic ring interaction with the oxygen-containing groups of pectin.

3.2. Iodine containing PCP.

In order to increase the PCP biological activity and to obtain materials with soft prolonged antiseptic action, iodine containing PCP was considered. A diffusion doping method was used – saturation of films with iodine vapors at room temperature (Fig. 6, Table 5). Doping of films with iodine by diffusion depends on the type of pharmacophore introduced into the polymer matrix. It was found that the polymer matrix with drug substance more strongly absorbs and retains iodine compared to pure apple pectin. It is known that the introduction of organic acid into the polymer system significantly changes the state of the system through the appearance of stable hydrogen bonds and contributes to its iodine enrichment [30].

Determination of the mass fraction of iodine in the samples immediately after saturation and after desorption shows that besides native pectin, all modified samples retain a sufficient amount of iodine, up to20-40%, after desorption (Table 5, Fig. 6).Desorption curves show that there are at least 2 different iodine forms coexist in the samples. One form is rather volatile and can be easily removed from the sample by simple air exposure. It can be ascribed to molecular iodine. The other form is quite stable and doesn't leave the sample even after hundreds of hours of air exposure. It seems possible to assume that this form consists of I_3^- and some higher polyiodides. The existence of different iodine forms is also confirmed by iodometric titration of the samples after desorption (Table 5).

Iodine sorption and desorption curves of the PCP films were used to estimate the values of iodine diffusion coefficients. To determine the diffusion coefficient D a Stefan's approximation was used [31]. It states that at short times (up to M_t/M_∞ =0.5), the amount of substance diffused is proportional to $t^{1/2}$:

$$M_t / M_\infty = 4\left(Dt/\pi l^2\right)^{1/2},$$

where M_t denotes the total amount of diffusing substance which has entered the sheet at time t,

M_∞ - the corresponding quantity after infinite time,

t – time,

D – diffusion coefficient,

l – thickness of the film.

The diffusion coefficients were also calculated from the Crank's solution of Fick's second law of diffusion [31, 32]. For non-steady diffusion in a plane sheet with equal surface concentrations the following equation was obtained:

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} \exp\left\{-D(2n+1)^2 \pi^2 t / l^2\right\}.$$

Taking n=0 for late-time approximation results in:

$$\frac{M_t}{M_\infty} = 1 - \left(\frac{8}{\pi^2}\right) \exp\left(-D\pi^2 t / l^2\right).$$

These equations were used to determine D both for sorption and desorption processes. It should be noted that only molecular iodine was taken into account in calculations of diffusion coefficients during desorption. The results of calculations are shown in Table 6.

The calculations by both methods show quite similar results. The highest diffusion coefficient is observed for pure pectin. The introduction of bulk pharmacophores into the pectin polymer matrix contributesin a decrease of its free volume and, as a result, in a significant reduction of the diffusion coefficients. The smallest diffusion coefficient during sorption is observed for PC-5ASA. Probably the presence of three potentially active groups in 5-ASA molecule (amino, hydroxyl and carbonyl groups) leads to some steric obstacles to the iodine penetration into the sample by chelation with hydroxyl groups of pectin.

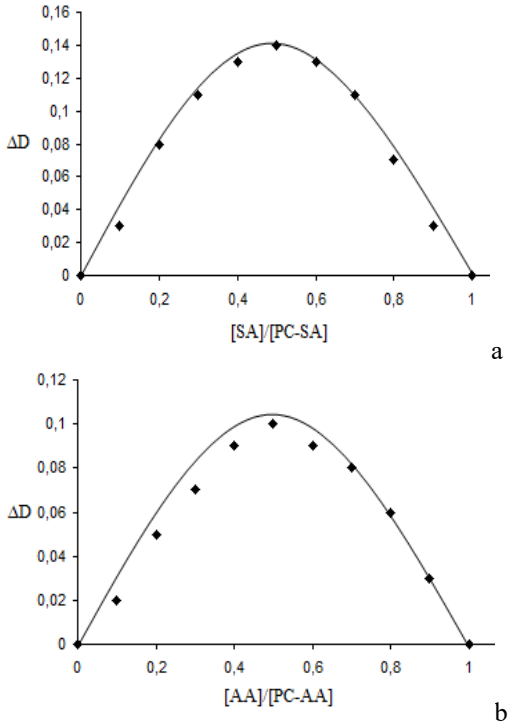


Figure 1. Dependence of the change in optical density on the composition of the isomolar solution for a mixture of PC and SA (a) and PC and AA (b); C=1·10^{-5}mol/l, λ=303 (a) and 304 nm (b), 25 °C. Water solution.

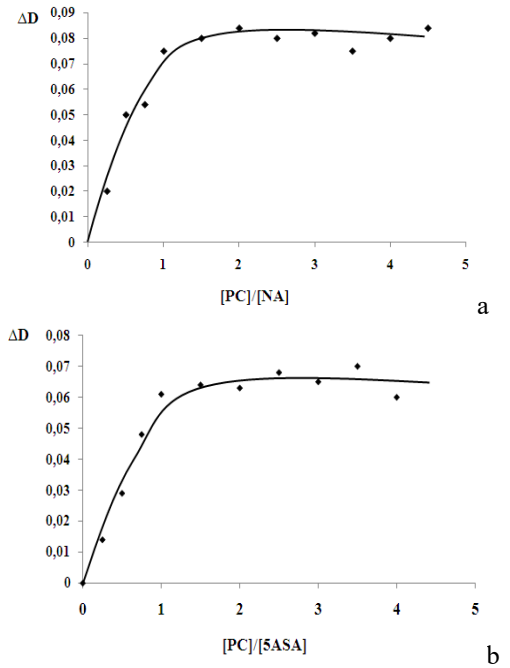


Figure 2. The saturation curve of the mixture of PC and NA (a) and PC and 5ASA (b); C=1·10^{-4}mol/l, λ=265 (a) and 310 nm (b), 25 °C, solvent – water.

For three samples (PC-SA, PC-AA and PC-NA) the diffusion coefficients values in the process of desorption are much smaller than in the sorption process. During desorption these samples contain a significant amount of iodine in various forms,

which also leads to a decrease in free volume and a diminishing in diffusion coefficients.

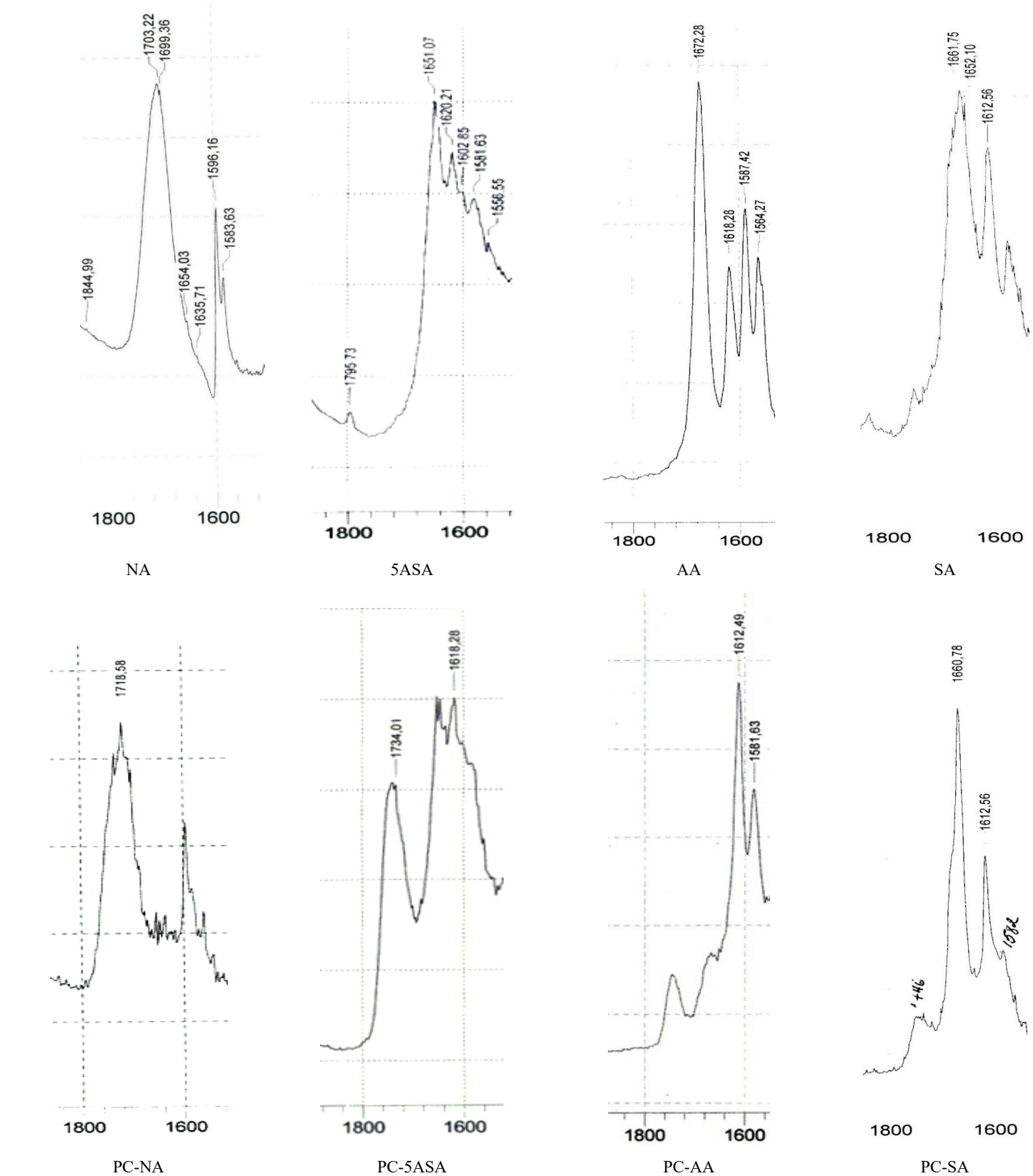
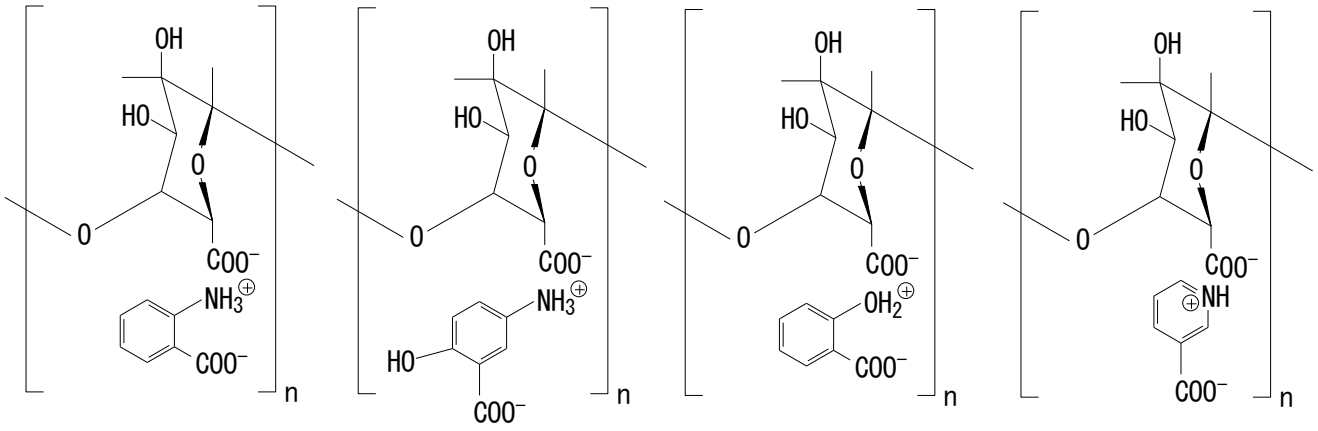


Figure 3.IR spectra in 1600-1800 cm^{-1} region of DS and their complexes with pectin.

For PC and PC-5ASA, the diffusion coefficients in sorption and desorption processes are almost identical. For pure pectin, this is quite expected result, since the amount of iodine incorporated into the polymer matrix is very small and can hardly affect the diffusion rate. The reason for PC-5ASA anomalous behavior is not so obvious. Perhaps some changes in the microstructure of the sample surface after doping play a role here (Fig.5, 7).

Desorption of iodine in water is accompanied by swelling and dissolving of the pectin matrix itself. The amount of iodine in water was controlled by intensity of AB at 290 nm (I_3^-) (Fig. 8).



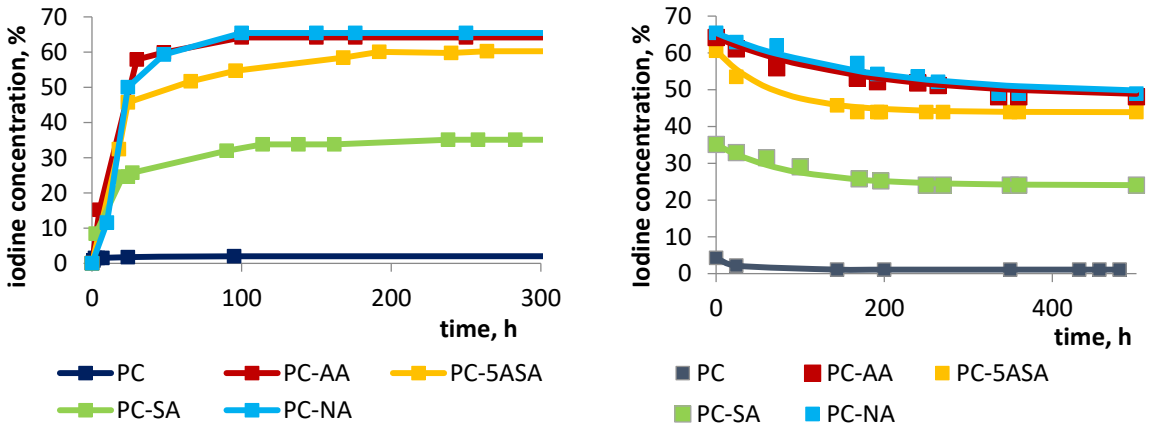
PC-AA PC-5ASA PC-SA PC-NA

Figure 4. Supposed structures of PC complexes with DS.

PC NA 5ASA

PC-NA PC-5ASA

Figure 5. Microstructure of polymer matrices, scale bar 100 μm.



a b

Figure 6. Iodine sorption (a) and desorption (b) curves for films of PCP complexes.

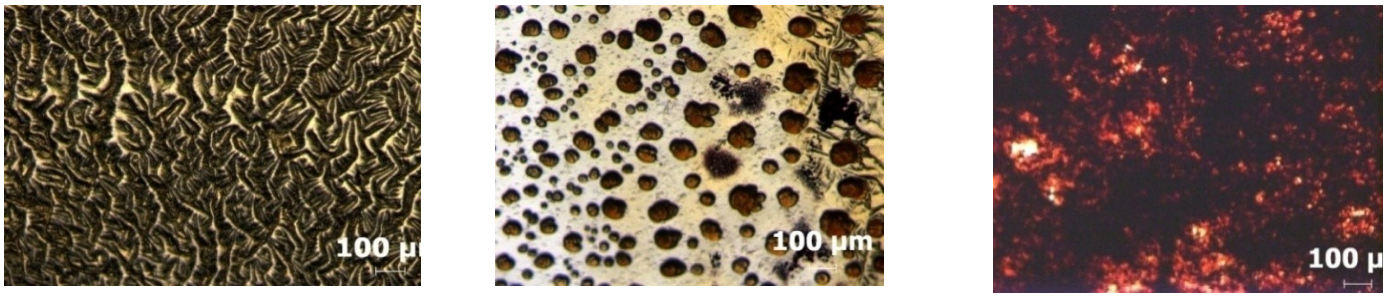
The complete release of iodine from the pectin film occurs after 25-30 minutes, while in samples with pharmacophores the time of iodine release increases up to 24 hours, providing a prolongation effect.

The compositions of PCP-I_2 complexes were determined by the method of isomolar series and molar relations (1:1) and stability constants (Table. 7). A stability series of iodine-containing pectin complexes during desorption in water looks as follows: PC-I_2<PC-AA-I_2<PC-5ASA-I_2<PC-SA-I_2<PC-NA-I_2.

The introduction of pharmacophore into the polymer matrix increases the stability of iodine-containing complexes by 50-250 times compared to the PC-I_2 system. IR spectra of iodine-PCP water solutions (Table 7) show that iodine interaction occurs on carbonyl and hydroxyl groups.

3.3. Biological activity of PCP.

The results of bacteriological studies of original and iodine-doped PCP films are presented in Table 8 and figure 9. The activity of the compounds was evaluated by the degree of inhibition of infectious agents growth in comparison with the control sample. As it can be seen from Table 8, the largest growth delay zone was observed in the PC-NA-I_2 sample. The results indicate the prospects of the use of these materials in medical practice that, along with the prolongation of the action and the lack of aggressiveness inherent in iodine, makes it promising to use them as antiseptic materials of mild action.



PC-iodine PC-NA-iodine PC-5ASA-iodine

Figure 7. Microstructure of polymer matrices doped with iodine, scale bar 100 µm.

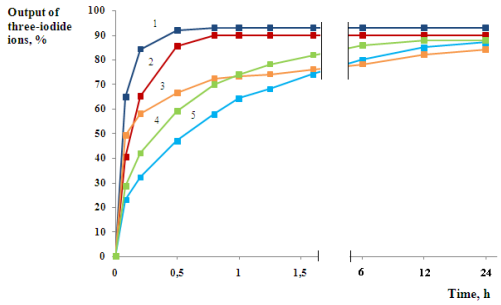


Figure 8. Kinetic curves of iodine ions release from the PCP films in water: 1 – PC, 2 – PC-AA, 3 – PC-5ASA, 4 – PC-SA, 5 – PC-NA. λ=290 nm, l=1.0 cm, T=25 °C.

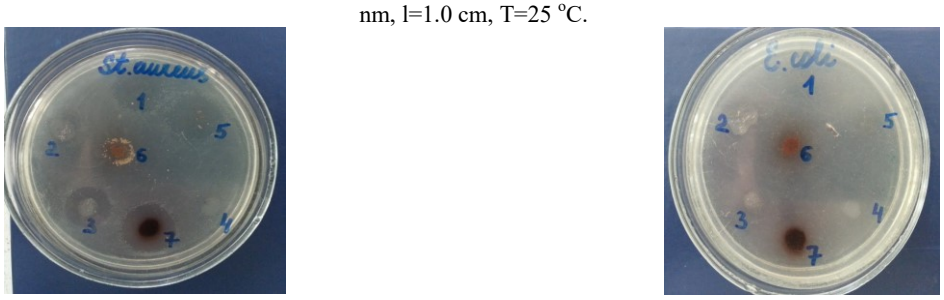


Figure 9. Inhibition zone of microorganisms growth *Staphylococcus aureus* and *Escherichia coli*; samples 1 – PC-I_2, 2 – PC-SA; 3 – PC-SA-I_2; 4 – PC-NA; 5 – PC-NA-I_2; 6 – PC-5ACA; 7 – PC-5ASA-I_2.

Table 1. Elemental composition of pharmacophore-containing pectins.

Sample	C,%		H,%		N,%	
	exp.	theor.	exp.	theor.	exp.	theor.
PC-AA	46.01	44.40	5.21	4.70	4.95	3.45
PC-5ASA	45.33	44.30	5.02	4.92	5.01	3.44
PC-SA	47.22	46.15	4.97	4.61	-	-
PC-NA	44.79	42.90	4.80	4.20	5.44	3.59
PC	40.25	42.11	5.49	4.86	-	-

Table 2. Physico-chemical characteristics of pectin interaction products with drug compounds.

Compound	$\beta_к \cdot 10^{-3}$, l/mol	λ_{max}, nm, H_2O	ν, cm^{-1}	α^{20}_D, (C 0.01; H_2O)	[η], dl/g
PC	-	210	3388 ν(OH), 1741 ν(C=O), 1104-1015 ν(C-O, C-C)	+180±2	2.3
PC-5ASA	2.8±0.1	310	3315 ν(OH), 1734 ν(C=O), 1101-1022 ν(C-O, C-C)	+52±2	0.8
PC-NA	4.0±0.2	265	3300 ν(OH), 1718 ν(C=O), 1114-1032 ν(C-O, C-C)	+115±2	3.5
PC-AA	2.7±0.1	304	3304 ν(OH); 1720 ν(C=O), 1103-1014 ν(C-O, C-C)	+47±1	1.1
PC-SA	2.0±0.1	303	3237 ν(OH); 1746 ν(C=O), 1100-1021 ν(C-O, C-C)	+84±2	0.9

Table 3. Structure of drug compounds with carbon atoms numeration.

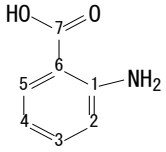
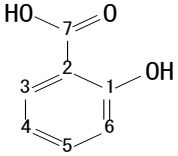
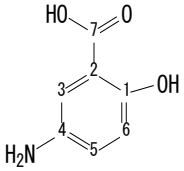
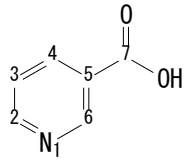
Compounds	
 **Anthranilic acid AA**	 **Salicylic acid SA**
 **5-aminosalicylic acid 5ASA**	 **Nicotinic acid NA**

Table 4. Values of chemical shifts ^{13}C CH-groups of individual substances and their complexes.

№C	AA	Complex PC-AA	Δδ, ppm	5ASA	Complex PC-5ASA	Δδ, ppm
C^1	146.40	146.78	0.38	153.41	153.73	0.32
C^2	118.24	118.09	0.15	116.81	116.87	0.06
C^3	131.08	131.05	0.03	123.22	123.45	0.23
C^4	120.70	120.77	0.07	136.81	136.10	0.70
C^5	132.29	132.20	0.09	120.15	120.19	0.04
C^6	118.86	118.58	0.28	117.90	117.69	0.21
C^7	175.34	175.63	0.29	175.28	175.21	-0.07
№C	SA	Complex PC-SA	Δδ, ppm	NA	Complex PC-NA	Δδ, ppm
C^1	159.60	159.60	0	-	-	-
C^2	117.88	117.77	0.11	142.96	143.43	0.53
C^3	134.03	134.03	0	126.83	126.74	0.09
C^4	119.35	119.35	0	142.40	142.85	0.45
C^5	130.47	130.47	0	135.38	135.39	0.01
C^6	116.28	116.28	0	145.78	145.36	0.42
C^7	175.38	175.38	0	168.14	168.58	0.44

Table 5. Maximum iodine content in samples after doping and after desorption.

The name of the sample	Iodine content of the sample		
	After doping [I_{gen}], % mass	After desorption	
		[I_{gen}], % mass	[I_2], % mass
PC-I_2	4.2	1.1	0.6
PC-NA-I_2	65.5	33.0	14.4
PC-AA-I_2	65.5	33.0	18.6
PC-5ASA-I_2	60.5	33.2	5.5
PC-SA-I_2	39.2	25.0	4.4

Table 6. Iodine diffusion coefficients.

Sample	Iodine diffusion coefficient D, 10^{-15} m^2/sec			
	Sorption		Desorption	
	Stefan	Crank	Stefan	Crank
PC	181.00	190.50	159.00	233.20

PC-5ASA	7.24	6.66	8.17	6.93
PC-SA	13.70	9.40	1.81	3.54
PC-AA	12.50	16.90	3.42	2.74
PC-NA	9.16	13.60	1.39	3.08

Table 7. Physical and chemical characteristics of aqueous solutions of the samples obtained.

Compound	IR spectra, ν, cm^{-1}	$\beta_k \cdot 10^{-3}$, l/mol
PC-I_2	3312 ν(OH); 1733 ν(C=O); 1149, 1024 ν(C-C, C-O)	0.7±0.1
PC-SA-I_2	3324 ν(OH); 1745 ν(C=O); 1155, 1018 ν(C-C, C-O)	69.0±3.0
PC-5ASA- I_2	3367 ν(OH); 1730 ν(C=O); 1135, 1014 ν(C-C, C-O)	6.4±0.1
PC-AA-I_2	3326 ν(OH); 1720 ν(C=O); 1100, 1005 ν(C-C, C-O)	6.2±0.1
PC-NA-I_2	3338 ν(OH); 1707 ν(C=O); 1114, 1032 ν(C-C, C-O)	190.0±15.0

Table 8. The zone of growth inhibition of microorganisms, mm^2.

Compound	*Staphylococcus aureus*	*Staphylococcus epidermidis*	*Escherichia coli*
I_2	12	13	12
PC-I_2	15	-	9
PC-SA	8	-	7
PC-SA-I_2	20	7	11
PC-NA	-	-	-
PC-NA-I_2	22	-	-
PC-5ASA	9	-	8
PC-5ASA-I_2	20	-	10
PC-AA	-	-	-
PC-AA-I_2	17	-	-

4. CONCLUSIONS

New complex compounds based on apple pectin and pharmacologically active organic acids (nicotinic, salicylic, 5-aminosalicylic and anthranilic acids) were synthesized. It was shown that the apple pectin forms 1:1 complexes with selected organic substances (i.e. 1 drug molecules per 1 pectin monomer unit).The structures of the complexes obtained were suggested.

The conditions for obtaining stable iodine-containing films based on pharmacophores modified pectin have been developed. It was shown that the inclusion of organic pharmacophore in pectin matrix leads to an increase in iodine content in polymer by 17–30 times and makes it possible to obtain pectin films not only with a high iodine content but also with its controlled and prolonged release. Iodine diffusion coefficients during sorption and desorption processes were calculated.

According to the results of microbiological tests, it was found that film materials based on the PC-SA-I_2, PC-5ASA-I_2, PC-NA-I_2systems are better in antibacterial activity to the PC-$I_2$by 1.3-1.5 times (depending on the structure of the modifying pharmacophore). Thus, our approach makes it possible to obtain iodine-containing film materials based on pectin polysaccharides modified with pharmacologically active acids that have an antimicrobial effect.

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