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MODIFICATION OF THE SOLUBILITY OF BENZIMIDAZOLE DRUGS ON MECHANICAL TREATMENT WITH PECTINS

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The change in the solubility of some benzimidazole drugs on their mechanical treatment with pectins has been investigated. It has been shown that the rate of desorption of a drug depends both on its structure and on the nature of the pectin.

Plant pectins are promising polymeric carriers for medicinal substances [1]. The variety of their chemical structure enables the properties of drugs to be regulated by the interaction of the latter with pectin substances.

We have previously shown the possibility of varying the antihelminthic properties of a low-molecular-mass drug (medamin) by its co-grinding-activation with apple pectin [2]. In the present paper we consider the results of a study of the influence of the functional groups of the pectin and of the drugs on the solubility of the latter as a result of the mechanochemical interaction of some benzimidazoles [methyl benzimidazol-2-ylcarbamate (MBC), its hydrochloride (MBCHC), and its thiopropyl analog (TPMBC)] with pectins.

Benzimidazoles were chosen in order to determine the role of NH- and $\overset{+}{\text{N}}\text{H}$ groups and of a benzene substituent, while the pectins [pectic acid (NPK), industrial apple pectin (PK), and pectin peracetate (PPK)] were synthesized specially in order to obtain materials with definite functional groups.

Mechanical activation was achieved by the combined grinding of the benzimidazoles with the pectins in a ratio by weight of 1:2 in a planetary-centrifugal grinder with regulable energy stress. The complexes obtained were investigated by IR spectroscopy and also by solubility and dialysis tests.

The IR spectroscopic results (Figs. 1 and 2) enabled us to evaluate the change in the absorption bands both of the initial components during their grinding and of the mixtures of components before and after activation-grinding. On grinding, the pectins showed an increase in the intensity of the absorption bands and a clear separation of the signals, which indicated their partial degradation and also a cleavage of intra- and intermolecular hydrogen bonds (this was noticed particularly in the case of pectic acid, containing the active groups —COOH and —OH). No appreciable changes were observed in the IR spectra of the benzimidazoles on their grinding.

On the cogrinding of MBCHC with pectins, the absorption bands of the initial components in the IR spectra disappeared, the absorption bands of the characteristic functional groups (NH and $\overset{+}{\text{N}}\text{H}$ in MBCHC and of −OH and −C=O in pectin) changed their positions, and new bands appeared. On the mechanical treatment of a 1:2 mixture of MBCHC and NPK changes took place in the region of absorption of the $\overset{+}{\text{N}}\text{H}$ groups of the MBCHC (Fig. 1, curve 1: 2833, 3175, 3404 cm^{-1}) and of the OH groups of the NPK (Fig. 1, curve 2: 3280 cm^{-1}). On the mechanical treatment of MBCHC and NPK the absorption bands of the methoxycarbonyl groups of MBCHC at 1753 and 1632 cm^{-1} were transformed into a weaker one at 1753 cm^{-1}. The absorption band of the C—O groups of the pectin also underwent changes – the band at 1638 cm^{-1} disappeared. Changes were observed in the positions of the characteristic bands of both the MBCHC and the NPK in the 1000-1600 cm^{-1} region. It follows from what has been said that the shift in the absorption band of the $\overset{+}{\text{N}}\text{H}$ groups of MBCHC from 3404 to 3385 cm^{-1}, and the disappearance of the sharp absorption bands of the OH groups and C=O groups of the pectin indicate the formation of $\overset{+}{\text{N}}\text{H}\cdots\text{OH}$ and $\overset{+}{\text{N}}\text{H}\cdots\text{O}{=}\text{C}$ hydrogen bonds (Fig. 1, curve 3).

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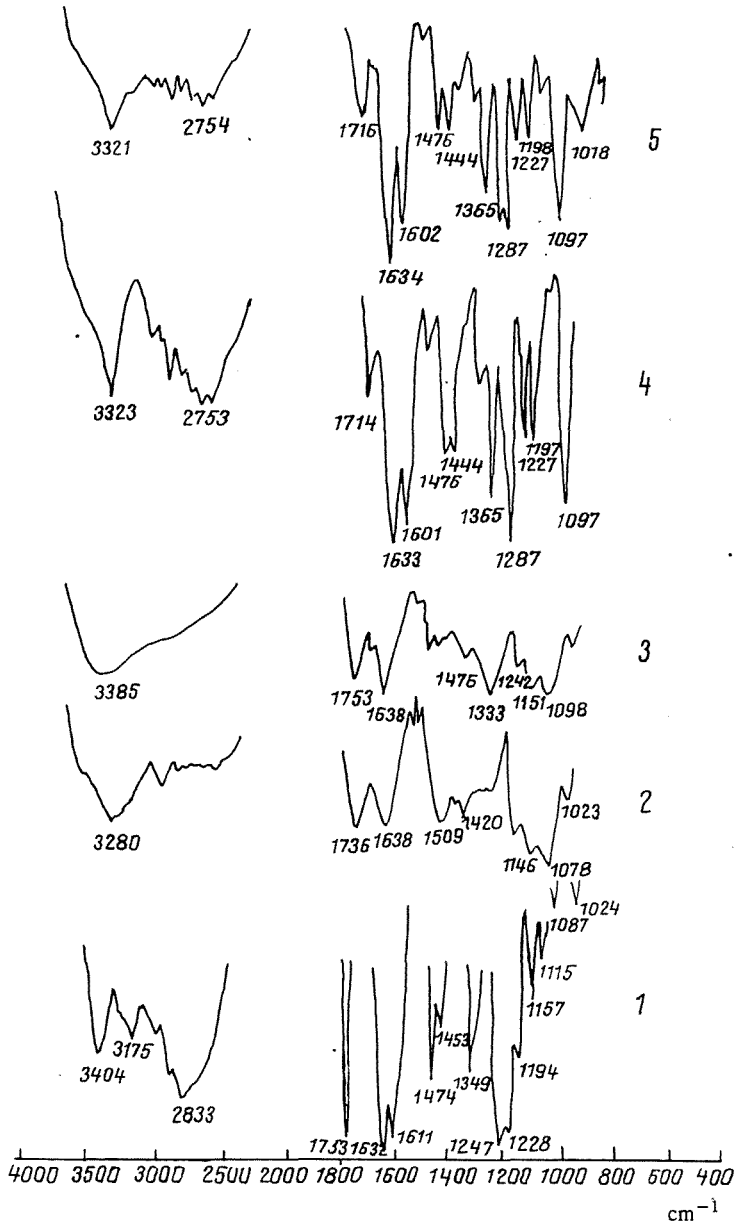

Fig. 1. IR spectra of MBC and MBCHC and their mixtures with NPK treated in an AGO-2U mill (40 g, module 1:7, 10 min). 1) MBCHC; 2) NPK; 3) MBCHC:NPK (1:2); 4) MBC; 5) MBC:NPK (1:2)

Analogous considerations apply to the MBC:NPK (1:2) system (Fig. 1, curves *2, 4,* and *5*). Characteristic for MBC are absorption bands at 3323 cm^{-1} ($\overset{+}{\text{N}}$H group) and 1714 and 1633 cm^{-1} (C=O group) (Fig. 1, curve 4). On the mechanical treatment of the mixture (Fig. 1, curve 5), the bands characteristic for the C=O groups of the NPK disappeared but the absorption bands of the methoxycarbonyl groups scarcely changed (or, rather shifted upfield: 1716 and 1634 cm^{-1}. respectively). This permits us to state that complex-formation takes place more feebly in the MBC:NPK (1:2) system than in the MBCHC:NPK (1:2) system; i.e., the $\overset{+}{\text{N}}$H group of MBCHC participates in complex-formation preferentially.

An investigation of the IR spectra of pectin (PK) with benzimidazoles showed that absorption bands at 3280 cm^{-1} (OH groups) and 1736 cm^{-1} are characteristic for PK, and these disappeared on the combined mechanical treatment of PK and MBCHC (Fig. 2, curve 2). Moreover, under these conditions the absorption band of the $\overset{+}{\text{N}}$H group of MBCHC shifted from 3404 cm^{-1} (Fig. 1, curve 1) to 3343 cm^{-1} (Fig. 2, curve 2) and the absorption band of the methoxycarbonyl groups underwent slight changes (compare Fig. 1, curve 1, and Fig. 2, curve 2). Taken together, these facts indicate complex-formation in the MBCHC:PK (1:2) system through H-bonds between the NH group of the MBCHC and the C=O groups of the pectin, and

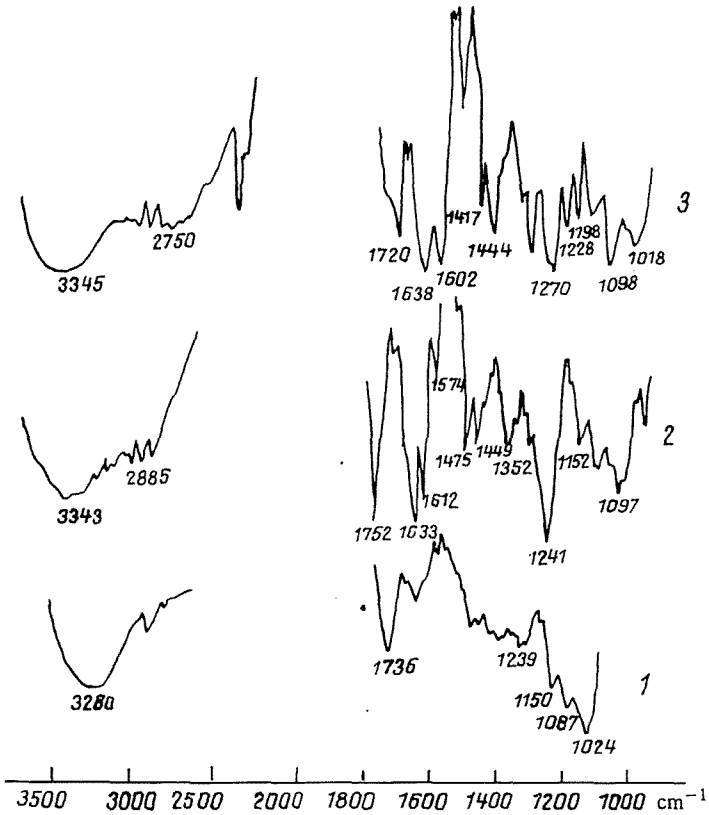

Fig. 2. IR spectra of pectin and its mixtures with MBC and MBCHC treated in the AGO-2U (40 g, module 1:7, 10 min). 1) PK; 2) MBCHC:PK (1:2); 3) MBC:PK (1:2)

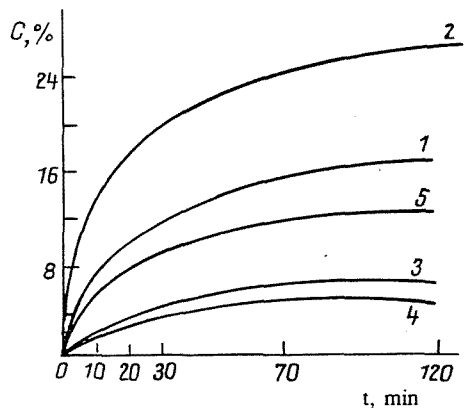

Fig. 3. Dynamics of the desorption of MBCHC from samples treated in the AGO-2U (40 g, module 1:7, 10 min): 1) MBCHC (init.); 2) MBCHC (ground); 3) MBCHC:PK (1:2); 4) MBCHC:NPK (1:2); 5) MBCHC:PPK (1:2).

also between $\overset{+}{N}H$ (MBCHC) and OH (PK). In addition, it is impossible to exclude the formation of an H-bond of the type of (PK) HO···O=C (MBCHC).

Analysis of the IR spectra of the mechanically treated mixtures MBCHC:PPK (1:2) and MBC:PPK (1:2) revealed no appreciable changes either in the region of $\overset{+}{N}H$ groups or in that of C=O groups. Furthermore, a shift in the absorption band of the C=N groups of the benzimidazoles showed the absence of an influence of other bands upon it. Thus, complete esterification of the pectin molecule leads to a substantial fall in its capacity for forming complexes with benzimidazoles.

TABLE 1. Rate Constants for the Diffusion of MBC, MBCHC, and TPMBC from Their Polycomplexes with Pectins

Sample	Constant	Sample	Constant
MBC (init.)	0.60±0.01	MBCHC : NPK	0.28±0.01
MBC (ground.)	0.73±0.01	MBCHC : PPK	0.80±0.01
MBC : PK	0.05±0.005		
MBC : NPK	0.01±0.01		
MBC : PPK	0.10±0.01	TPMBC (init.)	0.64±0.01
		TPMBC (ground.)	0.70±0.01
MBCHC (init.)	0.85±0.01	TPMBC : PK	0.08±0.005
MBCHC (ground.)	1.15±0.05	TPMBC : NPK	0.09±0.005
MBCHC : PK	0.51±0.01	TPMBC : PPK	0.06±0.005

Summarizing the IR-spectral results it is possible to speak of the formation of complexes of MBCHC with pectins through hydrogen bonds between $\overset{+}{N}H$ (MBCHC) and the C=O and OH groups of the pectins. The strongest complex is MBCHC:NPK (1:2), since it is here that substantial changes in the spectra are observed. The polycomplex MBCHC:PK (1:2) is less strong, since here there is hindrance through steric factors (although the ester group contains the potentially active carbonyl C=O, it is bulkier than the carboxy group in pectic acid). The MBC:PPK (1:2) complex is weaker, since here the hydroxy groups of the galacturonic acid ring are excluded from the sphere of interaction, and all the carboxy groups are esterified.

A comparison of the changes in the IR spectra of MBCHC and MBC (see Figs. 1 and 2) suggests that the $\overset{+}{N}H$ group takes part in complex-formation preferentially. Analogous conclusions follow from a comparison of the IR-spectral results for MBCHC and TPMBC and their polycomplexes.

A study of the dynamics of the desorption of MBCHC from its mechanically treated mixtures with PK, NPK, and PPK has shown (Fig. 3) that the best complex-formation takes place in the case of MBCHC:NPK (1:2); namely: the proportion of the MBCHC passing through a semipermeable partition in 120 min amounted to 4.6% (curve *4*), while in the cases of PK and PPK this proportion was 5.8 and 12.5% (curves *3* and *5*), respectively. A comparison of these results with the diffusion of the initial and ground MBCHC (curves *1* and *2*, 15.7 and 27.1%, respectively) permits the assumption that on the combined mechanical treatment of MBCHC with pectins complex-formation takes place through H-bonds between the active centers of the pectins and the $\overset{+}{N}H$ group of the MBCHC. The existence of such bonds leads to a slower liberation of the drug from the matrix of the polymer and its passage through a semipermeable membrane. In the case of MBCHC itself, however, the rate of penetration of the drug is considerable and it rises when the drug is ground. The results obtained show the possibility of regulating the rate of desorption of low-molecular mass drugs by their grinding or combined grinding-activation with various modified pectins.

The mathematical treatment of the results has permitted us to determine that the rates of diffusion of MBC, MBCHC, and TPMBC obey a 1st-order equation (Table 1).

It can be seen from Table 1 that a prolongation of the desorption and diffusion of the drugs through a semipermeable partition (in the case of their co-grinding-activation with pectins) and a high rate of diffusion of the ground drugs in isolation are also characteristic for the other benzimidazoles (MBC, TPMBC) and their mechanically activated mixtures.

EXPERIMENTAL

MBC and MBCHC were synthesized as in [3] and [4], respectively; **TPMBC was obtained** according to [4]; **industrial pectin was obtained** from the Tashkent cannery [5].

Preparation of Pectic Acid (NPK). PK (10 g) was treated with an alcoholic solution of alkali until the required degree of saponification of the ester bonds had been achieved. The resulting precipitate was washed to neutrality with aqueous alcohol, and the residual amount of ash substances (inorganic salts) was eliminated with an aqueous-alcoholic solution of HCl. The residue was dehydrated with alcohol and was dried at 80 ± 5°C. The yield of product was 5.8 g.

Preparation of Pectin Peracetate (PPK). Pectic acid (10 g) was dissolved in pyridine (100 ml) over 2 h, and the solution was heated at 40°C. Then 20 ml of acetic anhydride was added and, after 1 h, another 80 ml of acetic anhydride, with

constant stirring. The reaction mixture was poured into ice water. The precipitate that deposited was separated off, washed with water and with alcohol, and dried over P_2O_5. The yield of product was 6.0 g.

The grinding and activation of the benzimidazoles with the pectins was carried out in an AGO-2U planetary-centrifugal grinder-activator (Gefest, St. Petersburg) in metallic drums lined with polytetrafluoroethylene. Agate spheres were used as grinding bodies.

Grinding of MBC. The drum was charged with 1 g of MBC and 7 g of spheres (module 1:7), and the substance was ground in the mill at an energy stress of 40 g for 10 min.

The grinding of the MBCHC and the TPMBC was carried out similarly.

Grinding of the MBC-Pectin Composition:

a) the drum was charged successively with 0.5 g of MBC, 1.0 g of PK, and 10.5 g of spheres (module 1:7) and the mixture was subjected to grinding-activation at an energy stress of 40 g for 10 min;

b) the drum was charged successively with 0.5 g of MBC, 1.0 g of NPK, and 10.5 g of spheres, and the mixture was subjected to a 10-minute mechanical treatment at an energy stress of 40 g;

c) the drum was charged with 0.5 g of MBC, 1.0 g of PPK and 10.5 g of spheres, and the mixture was treated at 40 g for 10 min.

The grinding-activation of the MBCHC and the TPMBC compositions with pectins was carried out similarly.

Transmission and diffuse-reflection IR spectra were recorded on a Perkin–Elmer single-beam Fourier IR spectrometer (model 2000, 100 scans, resolution 4 cm^{-1}).

Dynamics of the Desorption of MBC from Its Polycomplexes with Pectins. A cell with a semipermeable partition was charged with 0.04 g of the MBC:NPK (1:2) polycomplex. The cell was lowered into a beaker containing 0.1 N HCl (gastric juice medium) and the solution in beaker was stirred with a magnetic stirrer (speed of rotation 100–120 r.p.m.) Aliquots of the solution were taken after predetermined intervals of time (from 10 min to 2.0 h). The amounts of MBC desorbed through the semipermeable partition were determined spectrophotometrically on a SF-46 instrument at $\lambda = 282$ nm (see Fig. 3).

The dynamics of the desorption of MBC from its polycomplexes with PK and PPK and also of MBCHC and TPMBC from their polycomplexes with PK, NPK, and PPK were studied similarly.

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