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PREPARATION AND PHYSICOCHEMICAL PROPERTIES OF POLYMERIC COMPLEXES OF METHYL BENZIMIDAZOL-2-YLCARBAMATE WITH APPLE PECTIN

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Polymeric complexes have been obtained by the combined mechanical treatment of enzyme-treated apple pectin and methyl benzimidazol-2-ylcarbamate, and their physicochemical properties have been studied.

Benzimidazoles continue to remain a promising class of anthelminthic drugs. Because of the low solubility in water and organic solvents of the majority of them, they are employed mainly as contact drugs, which restricts the sphere of their use and the efficacy of their action. Various methods of improving the solubility of benzimidazole anthelminthic drugs are known [1]. The mechanochemical method of activating a mixture of a drug and a hydrophilic polymer in grinder-activators with a high energy loading, enabling polymeric complexes (PCs) to be obtained simultaneously with dispersion [2-4], must be regarded as promising.

In the present paper we give results on the preparation of PCs and on the investigation of the physicochemical properties of PCs based on methyl benzimidazol-2-ylcarbamate hydrochloride (MBCHC) and enzyme-treated apple pectin (EAP), which is a highly esterified water-soluble pectin [5].

The solid-phase mechanochemical treatment of MBCHC was carried out in a planetary-centrifugal grinder-activator, with variations in its energy loading and in the time of activation. The formation of a PC was confirmed by IR spectroscopy which showed that in the mechanoactivation products the absorption bands of the initial components (in particular, the absorption bands of MBCHC: 3406, 3167, 2832, 1753, 1247 cm^{-1}) had disappeared or shifted and new bands had appeared at 1332 and 1096 cm^{-1}. As noted previously, [3] the formation of PCs takes place through the formation of hydrogen bonds between the functional groups of the initial components — namely, between the NH groups of the MBCHC and the carboxy groups of the EAP.

It is known that, on mechanical treatment in grinders, natural and synthetic polymers undergo degradation [4]. A study of the viscosities of solutions of EAP and its PCs has shown that solutions of the pectin exhibit an anomalous course of the dependence of the reduced viscosity on the concentration; i.e., solutions of the pectin possess the properties of weak polyelectrolytes. However, these properties gradually weaken with an increase in the mechanical loading, which is explained by a decrease in the molecular mass of the pectin as a result of degradative processes occurring under the action of mechanical stress (Fig. 1).

No such relationship was observed for solutions of the PCs, which confirmed the existence of an interaction between the active groups of the MBCHC and the EAP (Fig. 2).

Calculation of the molecular masses (MMs) of aqueous solutions of pectins and their polycomplexes obtained under various grinding regimes showed that the EAP was degraded more readily than the PCs (Table 1), obviously as a consequence of the stabilizing role of the MBCHC as a component of the polymers [4].

For the mathematical treatment on a computer of the results obtained, we used Fuoss's equation [6], which permitted the calculation of a measure of the effective volume of the pectin molecule (the constant A) and the strength of the electrostatic

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TABLE 1. Characteristic Viscosities [η] of Solutions of Pectin and its Complexes Obtained under Various Grinding-Activation Regimes

Pectin sample	[η]		MM of the pectin
	H_2O	in 0.1 N HCl solution	
Initial	1.84	0.90	19900
Ground at			
20 g	1.42	0.70	13000
40 g	1.09	0.68	5900
60 g	1.07	0.62	5400

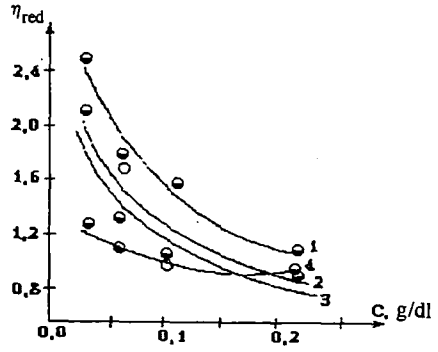

Fig. 1. Dependence of the reduced viscosity of a pectin solution on the concentration: 1) before grinding; 2-4) samples ground in the AGO-2Y at 20, 40, and 60g, respectively.

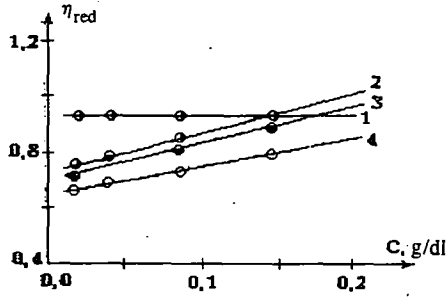

Fig. 2. Dependence of the reduced viscosities of solution on the concentration: 1) for a mechanical mixture; 2-4) for solution of the products of the activation-grinding of MBCHC and EAP at 20, 40, and 60g, respectively.

interaction between the pectin polyanion and the MBCHC counter-ion (the constant B) (Table 2). It follows from the figures of Table 2 that with an increase in the energy loading of the grinder the effective volume of the pectin molecule decreased and the strength of the electrostatic interaction increased, which is obviously a result of the dispersion and degradation of the EAP.

With an increase in the energy loading of the grinder, the solubility of the polycomplexes improved (Fig. 3), which agrees with the results of the viscometric studies. The results obtained were confirmed by determinations of heats of wetting (Fig. 4). With an increase in the energy loading of the activator during the production of the PCs the solubility both of the pectin samples and of their PCs improved. However, the heats of wetting of the PCs were less than the heat of wetting of the pectin, which is connected with the presence of a hydrophobic component — MBCHC molecules — in the PCs.

In order to predict a possible mechanism of the biological action of the PCs, we investigated the kinetics of the desorption of MBCHC from the PCs under conditions modeling a gastric juice medium. Some retardation of the liberation of MBCHC from the PCs was shown, which could lead to a retardation of the action of the drug (Fig. 5).

TABLE 2. Values of the Coefficients in Fuoss' Equation

Sample	A	B
Pectin	2.67	0.23
Pectin + MBCHC ground at		
20 g	2.21	0.24
40 g	2.03	0.34
60 g	0.81	0.83

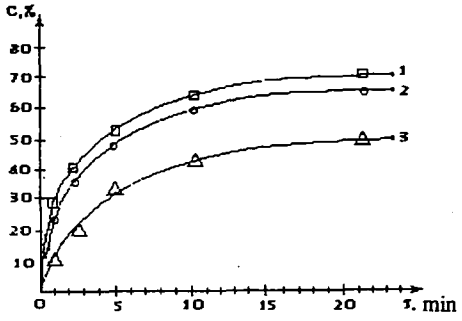

Fig. 3. Dynamics of the dissolution of MBHCH−EAP polymeric complexes obtained in the AGO-2Y at 60g (1), 40g (2), and 20g (3).

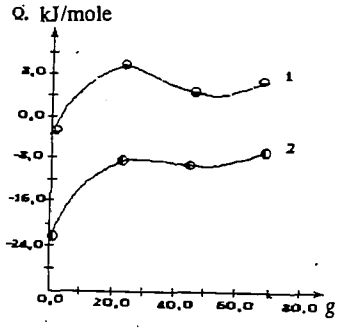

Fig. 4. Dependence of the heats of wetting of EAP (1) and its polymeric complexes with MBCHC (2) on the applied load during mechanical activation-grinding.

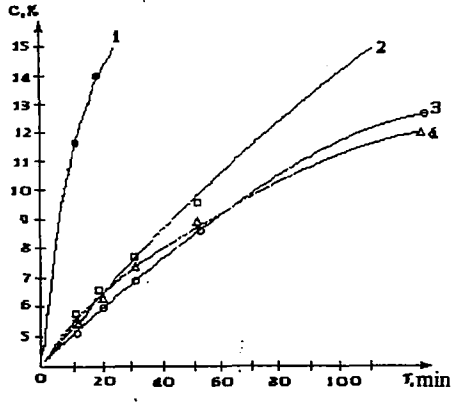

Fig. 5. Kinetics of the desorption of MBCHC (1) and of polymeric BMCHC−EAP complexes (2-4) obtained in the AGO-2Y at 40g (2), 20g (2), and 60g (3) (by dialysis at pH 1.2).

Thus, the mechanical activation–grinding of a mixture of MBCHC and EAP has given water-soluble polymeric complexes, and some of their physicochemical characteristics have been studied. The polymeric complexes obtained possessed a prolonging action.

EXPERIMENTAL

Mechanochemical treatment was carried out in an AGO-2Y planetary-centrifugal grinder-activator using PTFE-lined steel drums and agate spheres. Conditions of mechanical treatment: energy loading 20-60g, time of activation 30 min, ratio of the weight of the initial reactants and the weight of the grinding bodies 1:7.

Enzyme-treated apple pectin was obtained by the method of [5].

Heats of wetting were determined by Fuoss' method [6].

The viscosities of solutions of pectins and their complexes were studied in an Ubbelohde viscometer [7], which permits successive dilution of the solutions.

The molecular masses of the pectins were determined viscosimetrically by the method of [8].

The analysis of solubilities was conducted in an instrument of the rotating basket type [9]. The main working part of the instrument is a perforated basket of cylindrical shape with apertures having a diameter of 0.25 mm. During testing, the basket is rotated in the solvent (V = 900 ml, 0.1 N HCl) at the rate of 100 rpm. The sample under investigation (m = 0.01-0.05 g) was placed in the dry basket, which was immersed in the solvent so that its distance from the bottom of the vessel was (20 ± 2) mm. The vessel was closed with a lid and set in rotation. After predetermined intervals of time, samples of the solution were taken and were filtered through a Blue Ribbon filter. The active substance in the filtrate was determined quantitatively by spectrometry on a SF-46 instrument at λ 282 nm.

The desorption of the MBCHC for the polymeric complexes by the method of equilibrium dialysis was performed at 25°C in a cell with two chambers separated by a semipermeable cellophane membrane. The membrane did not interact with the components of the solution but ensured transport of the drug while being impermeable for the polyion and the counter-ions bound to it. The dialysis process was monitored for 2 h. After predetermined intervals of time, samples were taken for determining the concentrations of the drug in the cells of the dialyzer. The drug concentrations were determined spectrophotometrically in a SF-46 instrument.

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