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STUDY OF THE PROPERTIES OF MICROCRYSTALLINE CELLULOSE AND ITS POLYCOMPLEX WITH A BENZIMIDAZOLE DRUG AFTER MECHANICAL ACTIVATION

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The changes in the physicochemical properties of MCC on its being ground in an AGO-2U high-stress grinder-activator have been investigated. By the combined mechanical treatment in this activator of MCC and benzimidazol-2-yl methylcarbamate hydrochloride it is possible to achieve regulation of the solubility of the drug.

Microcrystalline cellulose (MCC) finds wide use in many sectors of the national economy (medicine, the food industry, perfumery, and coatings and paints) [1], and there has therefore been no weakening of scientific interest in the study of MCCs and the practical employment of those found useful.

The present communication reports an investigation of MCC as a polymeric matrix for obtaining prolonged-action drugs of the benzimidazole series having an antihelminthic action by grinding them together. The objects of investigation were MCCs obtained from cotton aerochemical lint (MCC-1) and from cotton cellulose (MCC-2) and also benzimidazol-2-yl methylcarbamate hydrochloride (BMCHC).

We have studied the influence of grinding on the properties of the materials selected when they were treated in an AGO-2U planetary-centrifugal grinder-activator. The problem was raised of elucidating the various factors (nature of the MCC, energy loading, time of activation, drug:MCC ratio, etc.) on the process of polycomplex formation.

Analysis of IR spectral characteristics, using the method of Nelson and O'Connor [2], enabled us to judge the change in the crystallinity indices of the MCC-1 (fall from 0.80 to 0.41) and MCC-2 (from 0.72 to 0.37) on their grinding in the AGO-2U. In addition, there were changes in the region of absorption bands of OH groups; namely, a broad band with a maximum at 3335 cm^{-1} due to a system of hydrogen bonds in the initial MCC had disappeared and a new absorption band with its maximum at 3400 cm^{-1} had appeared, witnessing the disruption of hydrogen bonds and the processes of degradation taking place. The above statements were confirmed by an increase in the intensity of absorption at 890 cm^{-1} due to the appearance of an OH group at C_1 [2]. The activation of the MCC on its grinding was shown by an increase in the intensity of an absorption band at 1640 cm^{-1} resulting from an increase in the amount of sorbed moisture in the MCC samples.

According to the results of differential thermal analysis all the samples of activated MCC had a monotypical nature, the DTA curves each containing two endothermic peaks at lower temperature ranges (300-335°C and 415-450°C), which indicates a fall in the thermal stability of MCC on its grinding.

By investigating the dissolution of BMCHC and its mechanically treated mixtures with MCC under conditions modeling gastric juice (Fig. 1) it was established that the co-grinding of the drug with MCC enables its solubility to be decreased through polycomplex formation, while under "severe" conditions of grinding a product with the lowest solubility is obtained. This is in harmony with reports [3] on the formation of solid solutions under co-grinding conditions when drug molecules are distributed monomolecularly in the pores of the MCC and form hydrogen bonds with the OH groups of the MCC through their potentially active centers (in our case the NH groups of BMCHC).

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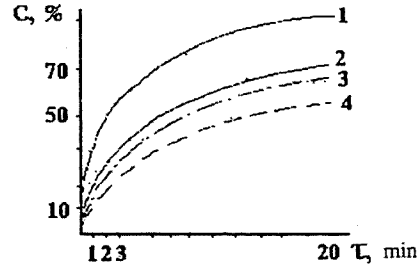

Fig. 1

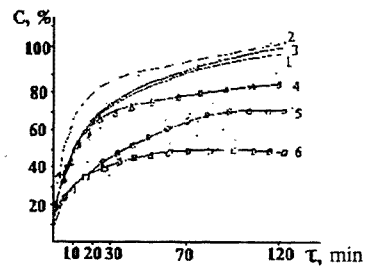

Fig. 2

Fig. 1. Solubility of BMCHC (1) and its mechanically treated mixtures with MCC-1 at 20 g (2), 40 g (3), and 60 g (4) in gastric juice.

Fig. 2. Dialysis of: unground BMCHC (1), ground BMCHC (2), BMCHC:MCC-1 = 1:1 (physical mixture) (3), BMCHCMCC-1 = 1:1 (mixture ground at 40 g) (4), BMCHC:MCC-1 = 1:2 (mixture ground at 40 g) (5), and BMCHC:MCC-1 = 1:3 (mixture ground at 40 g) (6).

An increase in the proportion of MCC in the BMCHC:MCC complexes from 1:1 to 1:3 (Fig. 2) led to a considerable retardation of the passage of the drug through a semipermeable partition when the polycomplexes were dialyzed in gastric juice.

Thus, we have investigated the grinding and activation of MCC from cotton aerochemical lint and from cotton cellulose and drugs (both separately and in a mixture), have studied the properties of these substances, and have shown that the difference in the properties of MCC-1 and MCC-2 levels out after grinding.

EXPERIMENTAL

Preparation of MCC-1 and MCC-2. Samples of the natural polymers were obtained by a unified technological scheme [1], with the only difference that cotton aerochemical lint was used to obtain the MCC-1, and bleached cotton cellulose for the MMC-2. Below, we give quality indices of the MCC samples obtained:

Quality index	MCC-1	MCC-2
Degree of crystallinity, %	82.5	85.0
Degree of polymerization (DP)	123	112
Proportion of water by weight, %	4.4	4.1
pH of a 1% solution	6.35	6.45
Proportion of ash by weight, %	0.49	0.12

The synthesis of BMCHC was achieved by dissolving BMC in aqueous hydrochloric acid and precipitating the hydrochloride by cooling the mother solution, according to [4].

The grinding and activation of the BMCHC with the MCC-1 and MCC-2 for 30 min at a ratio of 1:10 was carried out in an AGO-2U planetary-centrifugal grinder-activator (Gefect, St. Petersburg) in metal drums lined with PTFE. Grinding conditions: 20, 40, and 60 g. Agate spheres were used as the grinding bodies.

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

Thermal analysis was conducted on a Q-1000 derivatograph, and x-ray phase analysis on a DRON-3M diffractometer.

The dynamics of the desorption of BMBHC from its polycomplexes was investigated in a cell with a semipermeable partition. The cell was immersed in a beaker with 0.1 N HCl (gastric juice), and the solution was stirred in the beaker with the aid of a magnetic stirrer (stirrer speed 100-120 rpm). After predetermined intervals of time (from 10 min to 2.0 h) aliquots

were taken from the solution. The amount of BMCHC desorbed through the semipermeable partition was determined spectrophotometrically on an SF-46 instrument at a wavelength of 282 nm.

To evaluate solubility we used a rotating-basket instrument [5]. Quantitative analysis was conducted spectrophotometrically at a wavelength of 282 nm.

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