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MECHANICOCHEMICAL INTERACTION OF PLANT PROANTHOCYANIDINS WITH DRUGS

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The possibility has been studied of regulating the solubility properties of deoxypeganine by binding it with plant proanthocyanidins (katatsin, kavergal, yantapsin).

Plant proanthocyanidins (PAs) [1] are attracting researchers not only from practical but also from theoretical aspects in view of the specific features of their structure and the properties connected with them. Considering the peculiarities of the properties of PAs (polymeric nature, presence of potentially active OH groups in various positions in their structures (katatsin, yantapsin, kavergal)) [2-4] and the possibility of their activation on mechanical treatment (grinding), we have investigated the possibility of regulating some properties of drugs by grinding them together with PAs.

Our aim was to obtain drugs with regulable solubility in the form of polymeric complexes (PCs) by the mechanochemical interaction of these PAs with deoxypeganine hydrochloride (DOPHC) [5] in a planetary-centrifugal grinder-activator.

The synthesis of the PCs was achieved by the grinding-activation of a mixture of the initial substances (DOPHC, PA) in a ratio by weight of 1:2 with regulation of the time (from 10 to 30 min) and the energy intensity of grinding (from 20 to 60 *g*).

The formation of PCs through H-bonds between the potentially active NH group of the DOPHC and the OH groups of the PA was confirmed by IR spectroscopy [6, 7]. Thus, in the IR spectrum of the complex of deoxypeganine with yantatsin I (Fig. 1) [DOPHC—yantatsin (1:2)], a shifting of the absorption band of the OH groups from 3391 cm^{-1} (initial yantatsin) to 3385 cm^{-1} and also a decrease in the intensity of the band at 1678 cm^{-1} (C=N of deoxypeganine) were observed. By analogy with [8], the results obtained permit us to speak of the formation of a polycomplex between DOPHC and yantatsin through a monomolecular distribution of DOPHC molecules in a yantatsin matrix and the formation of hydrogen bonds between the OH group of yantatsin and the NH group of the DOPHC. Similar features were observed for the other polycomplexes studied.

An investigation of the properties of the PCs in solutions modeling gastric juice [9] showed that the solubility of PCs with DOPHC depended on the nature of the polymer (Fig. 2) and fell in the following sequence: DOPHC–katatsin (1:2) > DOPHC–kavergal (1:2) > DOPHC–yantatsin (1:2). The high solubility of the PCs is due to the fact that water rapidly penetrates within the reticular structure of the PC matrix in which the drug molecule is retained by hydrogen bonds with the PA molecules. Consequently, when PCs are dissolved, all the drug molecules can be liberated from the PCs simultaneously. If the concentration of the drug exceeds the solubility index, its excess crystallizes, as described in [10].

The desorption of DOPHC and its PCs and their diffusion through a semipermeable partition were investigated in 0.1 N HCl. The rate of desorption of DOPHC from the DOPHC–katatsin (1:2) polycomplex (Fig. 3) was considerably lower than that of the polycomplex with yantatsin, which agrees well with the structural features of the PCs themselves [7]. Kinetic investigations of the desorption processes showed that their rate followed the equation of first-order reactions (Fig. 4).

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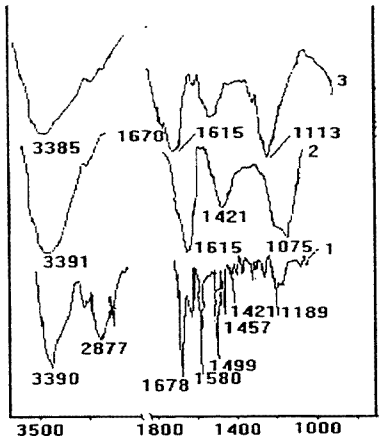

Fig. 1. IR spectra of DOPHC (**1**), yantatsin (**2**), and their PC (**3**).

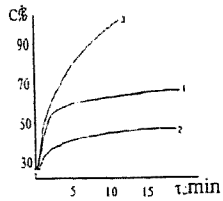

Fig. 2. Solubility of the PCs DOPHC:kavergal (1:2) [1], DOPHC:yantatsin (1:2) [2], and DOPHC:katatsin (1:2) [3].

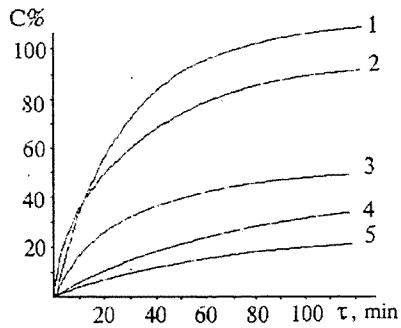

Fig. 3. Dialysis of DOPHC and its polycomplexes with proanthocyanidins: *1*) DOPHC (ground); *2*) DOPHC (initial); *3*) DOPHC:kavergal (1:2); *4*) DOPHC:yantatsin (1:2); *5*) DOPHC:katatsin (1:2).

Thus, we have shown the possibility of regulating the rates of dissolution and desorption of DOPHC by its mechanochemical complexing with proanthocyanidins.

EXPERIMENTAL

The grinding and activation of the DOPHC and PAs were carried out on a AGO−2U planetary-centrifugal grinder-activator (Gefest, St. Petersburg) in metal drums lined with PTFE. Agate spheres were used as the grinding bodies.

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

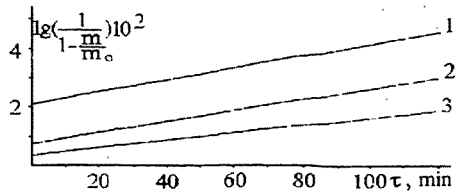

Fig. 4. Logarithmic dependence of the amount of dissolved DOPHC in its polycomplexes with proanthocyanidins: *1*) DOPHC:kavergal (1:2); *2*) DOPHC:yantatsin (1:2); *3*) DOPHC:katatsin (1:2).

Equilibrium dialysis was carried out at 25°C in a cell with two chambers separated by a cellophane semipermeable membrane. The membrane did not interact with the components of the solution and ensured the transport of the drug while being impermeable for the polyion and the counter-ions associated with it. The reaction was continued for 2 h. After predetermined intervals of time, samples were taken for checking the concentrations in the cells of the dialyzer. The concentrations of the drugs in the solutions were determined by a spectrophotometric method using a calibration graph. To simplify the calculation, the results of the dependence of D on the concentration of DOPHC were treated by the method of least squares on an IBM-PC computer.

To evaluate dissolution we used an instrument of the rotating basket type. The main working part of the instrument is a cylinder-shaped network basket with apertures having a diameter of 0.25 mm in which the sample under investigation (m = 0.04 g) is placed. During the trial, the basket is rotated in a dissolution medium (the volume of the dissolution medium is 900 ml) at the rate of 100 rpm. As the dissolution medium we used 0.1 N HCl (pH 1.1). The sample under test was placed in the dry basket, which was immersed in the dissolution medium in such a way that the distance to the bottom of the vessel was 20 ± 2 mm. The vessel was closed with a lid and set in rotation. After predetermined intervals, samples of the solution were taken, and these were filtered through a Blue Band filter. The active substance in the filtrate was determined by a spectrophotometric method. The amount of substances that passed into solution was determined for each medicinal form.

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