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MODIFICATION OF THE PROPERTIES OF ALLAPININ AND DEOXYPEGANINE BY THEIR MECHANICAL TREATMENT

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The change in the physicochemical properties of plant drugs — allapinin and deoxypeganine — on their grinding in an AGO-2U activator with a regulable energy loading have been studied.

It is known that plant substances, which are mainly physiologically active substances [1], are the active principles of many drugs [2].

At the present time there is a fairly large amount of information on the search for alkaloid-bearing plants, on the development of methods for isolating and separating alkaloids and determining their structures, on elucidating the dependence of the physiological action of an alkaloid on its structure, etc. Moreover, many alkaloids (lycorine, deoxypeganine, galanthamine, cytisine, allapinin, etc.) are manufactured as drugs and bioreagents [3]. However, information on the influence of a process of mechanical treatment (especially grinding) on the properties of alkaloids is almost completely lacking. At the same time, the stage of grinding is decisive in drug technology, since the efficacy of the majority of medicinal preparations is largely determined by their dispersity [4]. In view of the fact that the grinding of the active principles of drugs may lead to two opposite effects [5] — positive (increase in bioavailability, i.e., therapeutic effect, and improvement and standardization of the technological properties necessary at the stage of the medicinal form); and negative (degradation of the active principle, i.e., loss of activity of the preparation) —, it appeared of interest to investigate these consequences for a number of alkaloids as examples.

The aim of the present paper is a study of the changes in the physicochemical properties of the alkaloids deoxypeganine (**1**) and allapinin (**2**) [1] before and after grinding and an analysis of these effects for optimizing their grinding in the production of medicinal preparations.

The grinding of substances (**1**) and (**2**) was carried out on various types of comminutors (ball and hammer mills, disintegrators, etc.). The most suitable proved to be an AGO-2U planetary-centrifugal activator, in which the comminution of the drug material takes place in the field of three forces: two centrifugal forces and the Coriolis force. The centrifugal forces, acting on grinding balls and the material, are tens and hundreds of times greater than the force of gravity, thanks to which the energy stress of the activator, reaching 10 kW/dm, exceeds that of ball mills by 2-3 orders of magnitude [6].

An investigation of dispersity showed that (**1**) and (**2**), which are crystalline substances of medium hardness (4-5 on the Mohs scale) are readily dispersed in the initial period of grinding (Fig. 1). With an increase in the time of mechanical treatment an equilibrium arises between the forces of disruption and the forces of adhesion that are capable of agglomerating finely disperse particles into particles of larger diameter. In this case, the degree of dispersity of the particles of powder corresponds to such a state. It can be seen from Fig. 1 that grinding balls of small diameter are more effective for achieving a high degree of dispersity.

Optical analysis of the microstructures of initial and ground samples of (**1**) showed that, as grinding proceeded, the crystalline substance was converted into an amorphous state, the dispersity of the powder (80% fraction) decreasing from 100-120 to 11-15 μm (Fig. 2).

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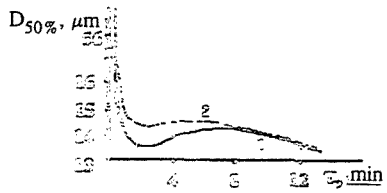

Fig. 1. Dependence of the degree of dispersity of DOPHC on the diameter of the grinding balls on its comminution in an AGO-2U: *1*) d = 4 mm; *2*) d = 8 mm.

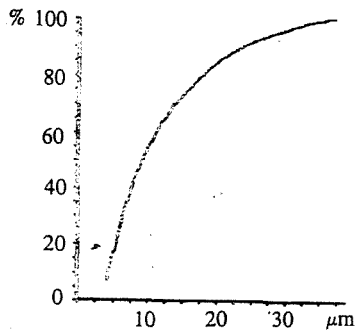

Fig. 2

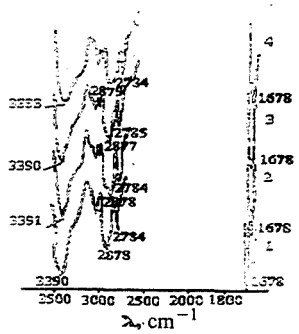

Fig. 3

Fig. 2. Curve of the sedimentation analysis of a ground sample of DOPHC.

Fig. 3. IR spectra of samples of DOPHC before grinding (*1*) and after grinding in an AGO-2U for 10 min at 20 *g* (*2*), 40 *g* (*3*), and 60 *g* (*4*).

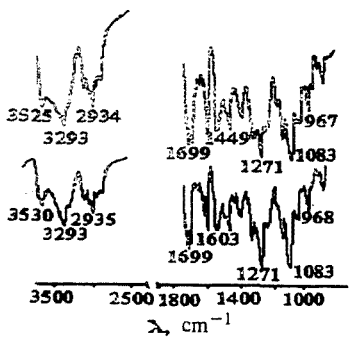

Fig. 4. IR spectra of samples of allapinin before grinding (*1*) and after grinding in an AGO-2U for 10 min at 60 *g* (*2*).

The IR spectra of the initial and ground samples of (**1**) and (**2**) (Figs. 3 and 4) had no substantial differences in the distribution of the characteristic absorption bands. Thus, a comparison of the IR spectra in the 3390 cm^{-1} region of sample (**1**) treated for 10 min at various energy stresses of the activator showed that there had been a breakage of intermolecular hydrogen bonds between the NH group of (**1**) and the OH group of the water of crystallization. The same pattern was characteristic for sample (**2**) in the 2935-3530 cm^{-1} region.

In the mass spectrum of (**2**) (Fig. 5) a peak (*m/z* 470/472) was detected that corresponded to a degradation product — bromolappaconitine, possibly formed by splitting out of anthranilic acid from (**2**), with the addition of a bromine atom at the position of its departure [1]. There have also been reports [7, 8] of phenomena of the degradation and hydrolysis of some drugs on their grinding. However, there has been no mention of the cleavage of C—C bonds (as in our case). The degradation of

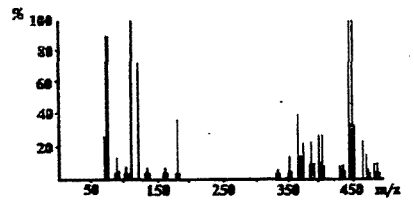

Fig. 5. Mass spectrum of allapinin ground in an AGO-2U planetary-centrifugal activator for 30 min at a ratio of 1:7 and 60 *g*.

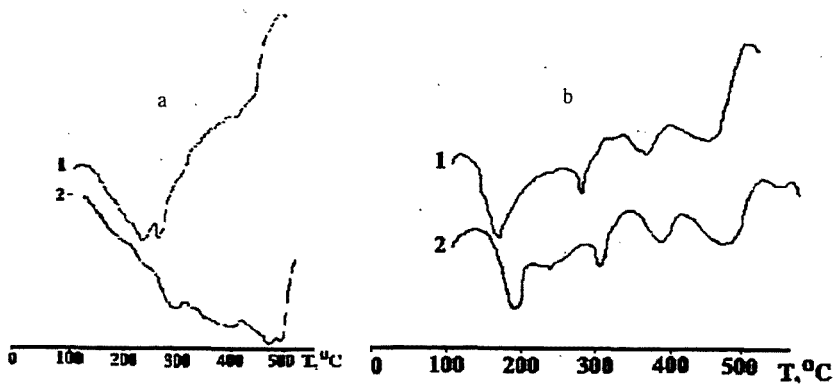

Fig. 6. DTA curves of the initial samples (*1*) and those ground in an AGO-2U for 30 min at 60 *g* (*2*) of: *a*) DOPHC; *b*) allapinin.

a drug the molecules of which contain water of crystallization is known. Sugimoto et al. [7, 8] understand by degradation the splitting out of a water molecule and, as a consequence, the breakdown of the crystal lattice of the drug.

The results of thermal analysis indicated substantial changes in the structure of (**2**) on grinding. Thus, while a thermogram of the initial sample (**2**) consisted of endothermic effects at 193 and 246°C and exo-peaks at 255, 281, and 360°C, the thermogram of a ground sample of (**2**) had only one endo-peak at 238°C (Fig. 6, *a*). A comparison of thermograms of initial and ground samples of (**1**) showed that on grinding it was converted into a thermally more stable form, as witnessed by a shift of all the thermal effect into the region of higher temperatures (Fig. 6, *b*).

X-Ray diffractograms of samples of (**1**) and (**2**) before and after grinding confirmed the results of optical microscopy, showing their partial amorphization. Thus, a diffractogram of an initial sample of (**1**) (Fig. 7, *a*) contained equatorial maxima of high intensity at 2θ = 5.04, 9.50, 11.62, 12.56, and 18.58°, while in a ground sample of (**1**) these maxima had either disappeared completely or had sharply decreased in intensity; moreover, new maxima had appeared at 2θ = 5.68, 8.50, 10.03, 13.12, and 14.30°. An analogous pattern was characteristic for samples of (**2**) (Fig. 7, *b*); the initial material had reflections at 2θ = 6.60, 10.92, 11.50, 18.80, 21.70, 22.88, and 23.78°, and the ground material at 2θ = 6.51, 8.34, 9.08, and 11.70°.

An investigation of the solubility of a sample of (**1**) under conditions modeling gastric juice showed that the initial rate of dissolution rose on grinding. This is explained by the decrease in crystallinity and the appearance of complete amorphization (see [5]). The results obtained show the possibility of regulating this property of a drug by grinding.

Thus, the grinding of the alkaloids selected leads to changes in a whole range of their properties, and a deep study of the consequences of grinding substances, especially drugs, is of great theoretical and practical significance.

EXPERIMENTAL

The grinding of deoxypeganine and allapinin was carried out on an AGO-2U planetary-centrifugal grinder-activator (Gefest, St. Petersburg) in metal drums lined with PTFE. Agate spheres were used as the grinding bodies.

Degrees of dispersity were determined on a Retsch Lumozed photosedimentometer. The Lumozed analytical system is based on the principle of gravimetric sedimentation and is one of the sedimentation–photometric methods. It is used for determining the granulometric compositions of particles and their distribution in the disperse state.

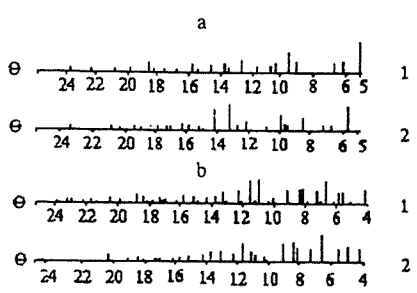

Fig. 7

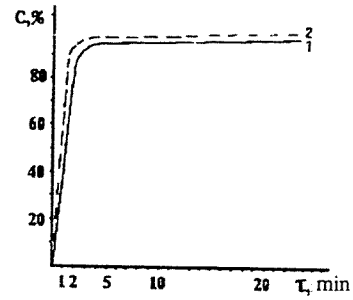

Fig. 8

Fig. 7. Reflections of initial samples (*1*) and samples ground in an AGO-2U for 30 min at 60 *g* (*2*) of: *a*) DOPHC; *b*) allapinin.

Fig. 8. Solubility curve of an initial sample of DOPHC (*1*) and of a sample ground in an AGO-2U for 30 min at 60 *g* (*2*).

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}).

To evaluate solubility we used an instrument of the rotating basket type [9]. Its main working part was a cylindrical network basket with apertures having a diameter of 0.25 mm in which the sample under investigation was placed (m = 0.04 g). During the trial, the basket was rotated in the dissolution medium (the volume of which was 900 ml) at the rate of 100 rpm. The dissolution medium used was 0.1 N HCl (pH 1.1).

The sample under test was placed in the dry basket, which was then immersed in the dissolution medium so that the distance to the bottom of the 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 Band filter. The active substance in the filtrate was determined by a spectrophotometric method. The amount of substance passing into solution was determined for each series of medicinal forms.

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

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