MECHANOCHEMICAL MODIFICATION OF DEOXYPEGANINE HYDROCHLORIDE BY POLYAMPHOLITE

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UDC 539.196:547.6:677.37

The solubility and dialysis of deoxypeganine hydrochloride and natural polyampholite were studied by IR spectra and x-ray diffraction analysis. Inclusion complexes form during mechanical treatment of a 1:1 mixture of deoxypeganine hydrochloride and natural polyampholite.

Key words: deoxypeganine hydrochloride, natural polyampholite, mechanical treatment, IR spectral investigations, x-ray diffraction analysis, solubility, dialysis, inclusion complex.

Deoxypeganine hydrochloride (DOPHC) is an anticholinesterase agent of plant origin [1].

Syntheses of DOPHC analogs were developed [2] in order to expand the spectrum of pharmacological activity of the preparation. The structure and properties of DOPHC were modified by polymers [3, 4].

The present article contains results from a study of mechanochemical modification of DOPHC by a natural polymer, polyampholite (PA) [5].

We considered the structural features of PA and DOPHC and hypothesized the formation of inclusion complexes (IC) by mechanical treatment, as previously described [6], and products from chemical reaction. These hypotheses were confirmed using IR spectroscopy and x-ray diffraction (XRD) analysis.

Mechanical treatment of the starting reagents (DOPHC and PA) and their mixture was performed in an orbital-centrifugal grinder-activator AGO-2U at variable energies and activation times.

IR spectral analysis of starting and ground samples of DOPHC showed partial cleavage of H-bonds and no decomposition or structural transformations [7].

XRD analysis indicates that the preparation is only slightly decrystallized in spite of the rather extensive grinding. Furthermore, treatment at 20 *g* strengthens the principal diffraction maxima. Such an effect was noted previously for other low-molecular-weight organic crystalline compounds. The strength of the diffraction maxima decreases markedly only after treatment at 60 *g* although all peaks remain in the diffraction pattern (at 18.7, 20.6, 21.6, 23.3, 25.1, 26.1, 28.2, 31.3, 34.9, 35.8, and 37.2°) and their positions do not change.

Thus, XRD analysis also indicates that mechanical treatment partially amorphizes DOPHC and destroys H-bonds which, in turn, lowers the melting point and increases the solubility. Data for the increased solubility of ground DOPHC have been reported [7].

IR spectra of PA have the following characteristic bands: 3292 cm^{-1} (OH and NH stretches), 2970, 2930 cm^{-1} (CH and CH_2 stretches), 1705 cm^{-1} (C=O stretch), 1631 cm^{-1} (CONH-amide I), 1515 cm^{-1} (CONH-amide II carbonyl) (δ NH + ν_{CO}).

Mechanical destruction in AGO-2U for 10 min at 60 *g* causes changes in the IR spectrum of PA. The frequency of the maximum for the OH and NH stretches decreases (3289 cm^{-1}) and the amide I band shifts to higher frequency (1658 cm^{-1}). The weak band at 1705 cm^{-1} disappears. This indicates that mechanical destruction affects the molecular structure of PA.

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0009-3130/01/3701-0065$25.00

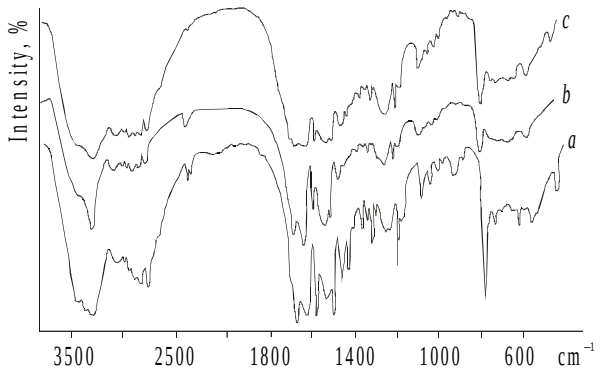

Fig. 1

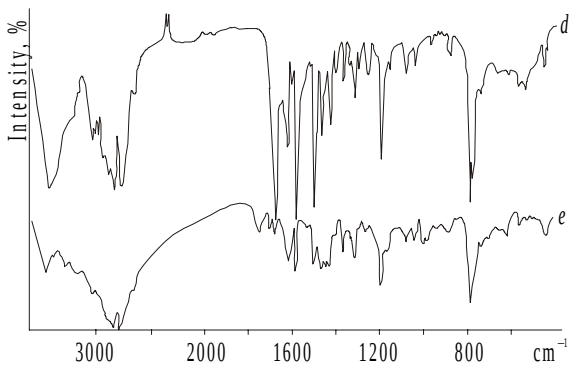

Fig. 2

Fig. 1. IR spectra of DOPHC:PA (1:1) mixtures, AGO, 10 min: 20 *g* (a), 40 *g* (b), 60 *g* (c).
Fig. 2. IR spectra: DOPHC (AGO, 60 *g*, 10 min) (d), difference spectrum DOPHC:PA inclusion complex (1:1, 60 *g*) - PA (60 *g*) (e).

XRD patterns of PA before and after grinding for 2θ = 10-40° also differ significantly. A peak at 2θ = 20.7° and a weaker one at 2θ = 25° are most characteristic of the PA patterns. The patterns show a slight rise for 2θ = 28-31°.

PA clearly becomes amorphous after various times of grinding in AGO-2U. The maxima at 2θ = 20.7° and 25° disappear. A diffuse ring with a peak at 2θ = 20.5° is observed. The results indicate almost complete amorphization of PA and formation of a new type of H-bond.

Treatment of DOPHC:PA (1:1) at an energy of 20 *g* and, especially, 40 and 60 *g*, causes noticeable changes in the IR spectra compared with those of the starting components (Fig. 1a-c, cf. Fig. 2d).

The shape of bands in the range 1500-1600 cm^{-1} changes and bands characteristic of DOPHC at 1678, 1580, and 1490 cm^{-1} dominate in IR spectra of a 1:1 mixture of DOPHC and PA after mechanical treatment at 20 *g*.

The redistribution of band strengths at frequencies due to OH, NH, and +NH groups, especially for the last (2500-3200 cm^{-1}), may be due to rearrangement of H-bonds (Fig. 1a).

IR spectra of DOPHC:PA (1:1) mixtures treated at 40 and 60 *g* differ markedly in the position, shape, and ratio of band strengths at 1000-1500 cm^{-1} from those of DOPHC (Fig. 2d).

Analogous shape changes, i.e., the appearance of blurred band envelopes is noted at 1500-1710 cm^{-1}, at which vibrations of the amide carbonyl, the PA COOH, and the heterocycle of DOPHC appear.

Thus, changes in the position, shape, and strength of IR bands of mechanically treated DOPHC:PA mixtures (Fig. 1a-c) suggest that an inclusion complex may form. This assumes that DOPHC reacts partially with PA during mechanical treatment of the mixture at an energy of 20 *g*.

A difference spectrum (Fig. 2e) obtained by subtracting spectra of the DOPHC:PA mixture (1:1, 60 *g*) and PA (60 *g*) is not identical to that of DOPHC, confirming that an inclusion complex forms during mechanical treatment of the 1:1 DOPHC:PA mixture.

Based on the appearance of a weak absorption band at 1745 cm^{-1} and a broad band at 1390-1500 cm^{-1}, part of the carboxylic groups are converted to the ionic form (COO^-) during reaction of PA and DOPHC. The weakening and constant frequency of the amide I (1631 cm^{-1}) and amide II (1515 cm^{-1}) bands in the difference spectrum (Fig. 2e) are consistent with a lack of interaction of the PA amide carbonyl and NH groups with the DOPHC +NH cation. Therefore, the presence of a strong band at 2250-3500 cm^{-1}, which corresponds to stretching of associated +NH groups, suggests that the DOPHC:PA inclusion complex is formed by H-bonds involving the +NH of DOPHC and the OH and COO^- of PA.

The similarity of the IR spectra of mechanically treated 1:1 DOPHC:PA mixtures (40 and 60 *g*) at 1000-1500 cm^{-1} (Fig. 1b and -c) indicates that the inclusion complex may already be formed at moderate AGO-2U activator loadings.

The solubilities of mechanically treated DOPHC:PA mixtures prepared at various energies agree with the IR data. Mechanical treatment of PA mixtures with drug causes slower dissolution of the sample under conditions simulating those of gastric juices when compared with starting drug, i.e., the dissolution process is prolonged (Table 1).

TABLE 1. Dynamics of DOPHC and DOPHC:PA (1:1) Inclusion Complex Dissolution After Mechanical Treatment at Various Energies in 0.1 N HCl (conc., %)

Energy, *g*	Duration of dissolution, min						
	0.5	1	2	5	10	20	30
DOPHC-initial	7.03	7.38	8.81	14.63	23.91	39.23	54.34
20	6.7	6.84	7.32	11.16	17.51	27.83	35.98
40	6.86	6.64	7.52	10.84	18.18	26.88	35.44
60	6.99	6.81	7.96	10.44	16.39	25.72	34.23

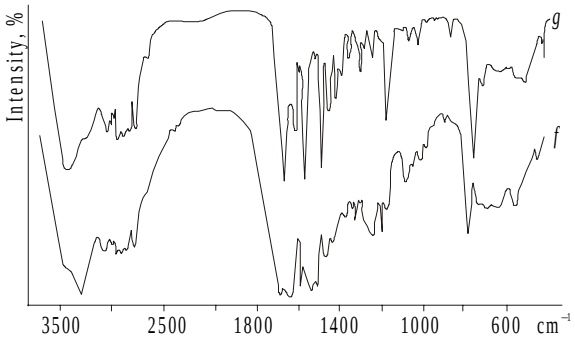

Fig. 3. IR spectra: DOPHC:PA (1:1) mixture, AGO, 40 *g*, 10 min: insoluble part (f), soluble part (g).

We explain this result by the formation of an inclusion complex, analogously to the literature [6], which is a system in which the drug and polymer are evenly mixed and H-bonds between the active groups of the reacting components are formed. For example, the solubility of the starting DOPHC was 54% in 30 min whereas the solubility of the 1:1 DOPHC:PA mixture obtained at 20, 40, and 60 *g* was 36, 35, and 34%, respectively.

Equilibrium dialysis [6] of the DOPHC:PA (1:1, 40 *g*) mixture and an IR spectral analysis of the soluble and insoluble parts were carried out for additional confirmation that an inclusion complex formed.

The analysis of these spectra suggests that practically pure DOPHC dissolves (possibly with a very small amount of extensively destroyed PA) (Fig. 3g).

The insoluble part gives a spectrum that is identical to that of the DOPHC:PA (1:1, 20 *g*) mixture in the range 1000-1500 cm^{-1} (compare the spectra in Fig. 1a and 3f). This indicates that DOPHC is sorbed by the polymer, i.e., formation of an inclusion complex.

Thus, the IR spectral investigations, XRD analysis, and solubility and dialysis study are consistent with formation of an inclusion complex during mechanical treatment of a 1:1 DOPHC:PA mixture.

EXPERIMENTAL

Mechanical treatment (grinding-activation) of DOPHC and its mixtures with PA was performed in an orbital-centrifugal AGO-2U activator (Gefest, Russia).

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

X-ray diffraction studies were carried out on a DRON-3M diffractometer with monochromatized Cu-Kα-radiation using 20-28 kV potential and 15-18 mA depending on the sample. Samples were prepared by pressing ground preparations into pellets. Exposures were taken in the range $2\theta = 10\text{-}40^{\circ}$.

Dissolution was evaluated using the literature method [8]. Quantitative analysis of the solutions was performed on an SF-46 spectrophotometer at $\lambda = 278$ nm.

Equilibrium analysis was carried out at 37°C in a two-compartment cell separated by a cellophane semipermeable

membrane. The membrane was inert to the solution components, enabled transfer of DOPHC, and was nonpermeable to polyions and counterions associated with them. Dialysis was monitored for 2 h. Samples were collected after certain time intervals to monitor the drug concentrations in the dialyzer compartments. The drug content was determined spectrophotometrically on an SF-46 instrument.

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