Chemistry of Natural Compounds, Vol. 33, No. 3, 1997

INTERACTION OF DRUGS WITH MICROCRYSTALLINE CELLULOSE AT THE MOLECULAR AND SUPERMOLECULAR LEVELS

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UDC 615.322:547.458.81:620.18

Various drug compositions based on plant substances (allapinin and microcrystalline cellulose (MCC)) have been studied before and after micronization with the aid of x-ray-diffraction, IR-spectroscopic, electron-microscopic and ESR methods of investigation. It has been shown that during the production of the drug compositions a physicochemical intermolecular interaction takes place that ensures a prolongation effect.

Microcrystalline cellulose finds wide use in the production of tablets [1-3]; its employment as a filler and binder permits improvements in the external form, shape stability, moldability, and physicomechanial properties of the tablets, a decrease in contamination by microorganisms, and a replacement of food products.

We have undertaken an attempt to evaluate the possibility of the interaction of MCC with various drugs in compositions. In the first place it was necessary to convince ourselves about any chemical interaction of these substances, since this may lead to extremely undesirable results, going as far as complete loss of the medicinal properties of a particular drug. There is no doubt that the probability of chemical reactions in the solid phase between MCC and various drugs is low. At the same time, the complex organic molecules of drugs contain various functional groups — hydroxyl, amino, carbonyl, carboxyl, and methoxyl groups and others — and this does not exclude the possibility of physicochemical interactions with cellulose at the primary and secondary hydroxyls with, in particular, the formation of H-bonds of different intensities. Moreover, the interaction of cellulose and drug components at the structural level is not excluded, and this may appreciably affect the properties of solid medicinal forms: strength, rate of disintegration in various media, etc.

In order to draw some preliminary conclusions on possible interactions of the above-mentioned type, samples of compositions including a drug and MCC have been investigated by the methods of x-ray diffraction, IR spectroscopy, and electron microscopy. Particular attention was devoted to model materials formed by two-component systems consisting of a drug and MCC in a ratio of 1:1. In order to avoid the repeated action of high pressures, the samples were carefully ground and deposited on a layer of a neutral substance (petroleum jelly), after which x-ray diffraction analysis was performed. X-ray diffractograms and IR spectra were taken of all the main components of the drug compositions — i.e., the pure substances, including the MCC and the drugs themselves, and also specially prepared model systems consisting of MCC and a drug (allapinin) in various ratios (by weight).

The x-ray diffractograms of allapinin and MCC contained different numbers of equatorial maxima differing in width and intensity, which showed the crystalline structure of these substances. For the drug preparations, about 20 equatorial maxima were observed. Each of the drug preparations had characteristic maxima not coinciding in their angular positions with the maxima of other compounds. Thus, for allapinin the most characteristic maxima of considerable intensity were those with 2θ = 13.2 and 18.2°. For cellulose, an appreciably smaller number of peaks was observed, at 2θ = 14.7 and 16.8°, and at 22.6 and 34.4°. The 22.6 and 24.4° peaks are the most useful for identifying cellulose (Figs. 1 and 2).

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 0009-3130/97/3303-0340$18.00 ©1997 Plenum Publishing Corporation

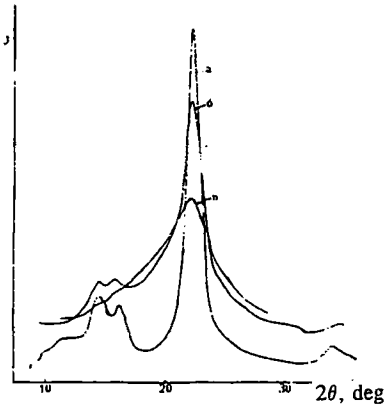

Fig. 1

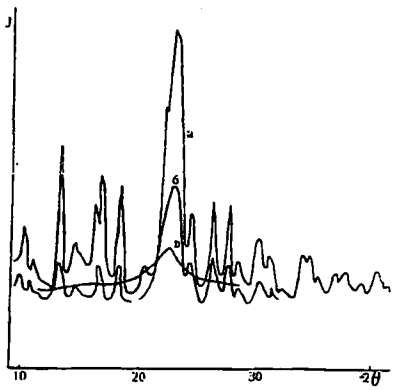

Fig. 2

Fig. 1. Diffractograms of MCC before (*a*) and after (*b*, *c*) micronization: *a*) init.; *b*) 30 min, 20 g; *c*) 30 min, 60 g.

Fig. 2. Diffractograms of the model system allapinin + MCC (1:1) before (*a*) and after (*b*, *c*) micronization. *a*) init.; *b*) 30 min, 20 g; *c*) 30 min, 60 g.

It must be mentioned that analysis of diffractograms of compositions consisting of several components is very difficult, since in a number of cases the maxima from different substances are superposed on one another. Moreover, small amounts of substances, even if of crystalline nature, are not detected. Our main attention was therefore devoted to model MCC–drug compositions.

Analysis of the diffractograms showed that, for the system under investigation, no new diffraction maxima had appeared. Thus, it may be assumed that no formation whatever of appreciable amounts of any new crystalline substance possessing a specific structure had taken place. This circumstance must be appraised positively, since an intense chemical interaction of drug and MCC could lead to unpredictable consequences. However, definite structural changes did nevertheless take place on the molding of the MCC with the drug. Above all, MCC present in the system somewhat lowers the crystallinity of any drug. This was shown by some broadening of many reflections (connected with a decrease in the dimensions of the crystalline sections) and a fall in their intensity that was particularly pronounced in the region of larger angles (from 25 to 45°). The latter is probably due to a disturbance of three-dimensional order in the crystalline regions of the drug.

A mutual influence of the MCC and the drug appeared in the 2θ = 14-17°, 21-24°, and 33-36° regions, i.e., where the main equatorial reflections of the cellulose were located.

For the MCC–allapinin model the most considerable changes in the diffractograms were those at 2θ = 14-17° and 21-24°. In pure allapinin there is a weak reflection at 2θ = 14.5° and a doublet of medium intensity with maxima at 2θ = 16.2 and 16.8°. For cellulose, more diffuse maxima were observed at 2θ = 14.7 and 16.6°. Diffractograms of the mixture showed a broadened cellulose reflection at 14.7° upon which were superposed a somewhat displaced 14.5° allapinin peak and the above-mentioned doublet of allapinin at 16.2, 16.8° with some change in the intensity ratio.

In the 21-24° region of a diffractogram of the mixture, in place of the intense reflections at 2θ = 21.7, 22.9, and 24.6° characteristic for allapinin, we observed a single intense maximum with a peak at 23° and a slight shoulder on the small-angle side of the peak at 2θ = 22.5°; i.e., a cellulose reflection suppressed reflections of the second component.

IR spectra of native cellulose, including MCC have been considered in detail in the literature [4].

Characteristic for IR spectra taken to investigate drugs is a large number of absorption bands, particularly in the 600-1800 cm^{-1} region, where the deformation vibrations of the functional groups present in these complex organic molecules appear. A full identification of these spectra is also given in the literature [5]. The assignment of particular absorption bands has therefore been made where necessary in the discussion of the results obtained (Fig. 3).

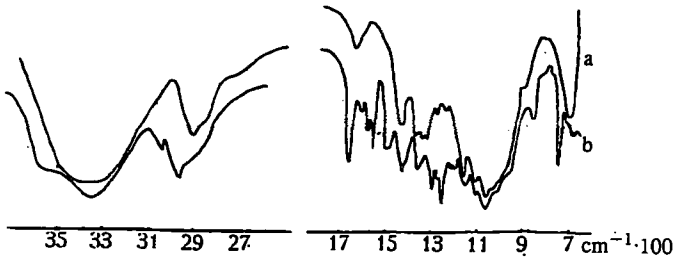

Fig. 3. IR spectra of the initial MCC (*a*) and the model system of allapinin + MCC (1:1) (*b*).

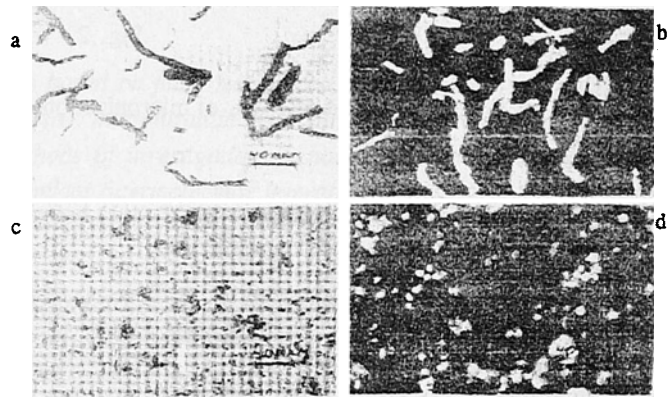

Fig. 4. Optical photographs of MCC before and after micronization in transmitted (*a, c*) and polarized (*b, d*) light: *a, b*) init.; *b, d*) 30 min, 60 g.

In the IR spectrum of allapinin with MCC the most pronounced changes from the spectra of the initial components had taken place in the region of 2800-3600 cm^{-1}, i.e., the stretching vibrations of OH and NH groups, both free and involved in hydrogen bonds. While in cellulose the OH groups give a very broad band covering the region from 3000 to 3700 cm^{-1} and in allapinin two discrete bands can be seen at 3300 and 3545 cm^{-1}, in the spectrum of the model preparation a fusion, as it were, of these bands had taken place with a fall in intensity in the 3300-3600 cm^{-1} range and a shift of the maximum to the right, which probably presupposes the formation of intermolecular H-bonds of allapinin with cellulose at NH and OH groups. The spectrum had also changed substantially in the region of stretching vibrations of $(CH)(CH_2)$ groups (2800-3000 cm^{-1}). The resolution was appreciably worsened and a broader diffuse band (as compared with pure allapinin) was observed.

The intensity of deformation vibrations in the 1750-1200 cm^{-1} (C=O, CH_3, CH_2OH) and of the C=O stretching vibrations (1300 cm^{-1}) had fallen somewhat. It is interesting that the deformation vibrations of the groups in the cellulose macromolecule scarcely appeared here — obviously because of a decrease in their intensity. However, in the 1000-1200 cm^{-1} interval the IR spectrum of the mixture corresponded more closely to the spectrum of cellulose — intense diffuse absorption was observed with several weak maxima corresponding to the stretching vibrations of ring C−C bonds and also to deformation vibrations of CH, OH, and CH_2 groups. Resolution had sharply deteriorated and the allapinin absorption bands in the 800-1000 cm^{-1} region had weakened, which may be connected with definite restrictions of the group vibrations of the corresponding functional groups.

Thus, it may be concluded that no new absorption bands appear in the IR spectra of mixtures of cellulose with allapinin. The main changes take place in the region of the stretching vibration of OH and NH groups involved in hydrogen bonds and also those of CH_2 groups, while in other regions of the spectra, in a number of cases a redistribution of the intensities or a weakening of absorption bands takes place. Consequently, no chemical interaction is revealed, but the possibility of the intermolecular interaction of MCC with drugs is fairly obvious, and this was also confirmed by structural studies (Figs. 4-6).

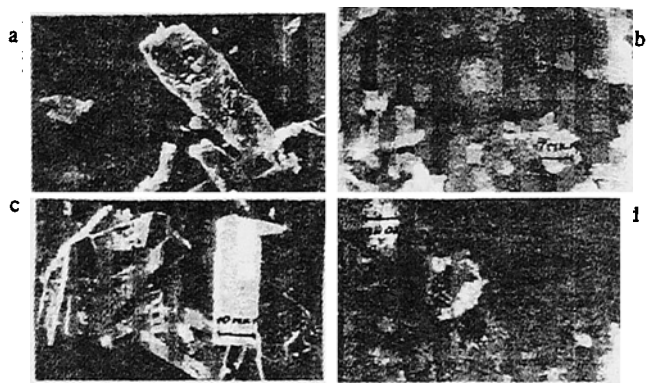

Fig. 5. SEM photographs of the initial components before (*a, c*) and after (*b, d*) micronization: *a, b*) init. MCC; *c, d*) allapinin.

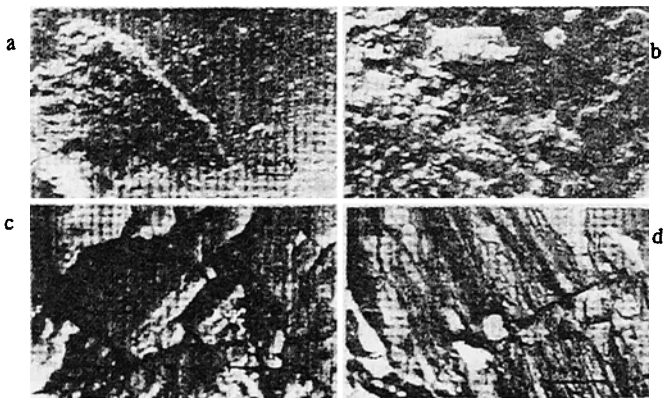

Fig. 6. SEM (*a, b*) and EM (*c, d*) photographs of tableted drugs in the initial state and with the addition of MCC: *a*) allapinin tablets; *b*) tablets of allapinin with MCC; *c*) replicas from the surface of allapinin; *d*) replicas from the surface of tablets of allapinin with MCC.

The mean dimensions of particles of MCC isolated from tablets had somewhat diminished, obviously as the result of further comminution during molding (80 μm in place of 100 μm). However, the isodiametric shape and external form of the MCC had undergone no appreciable changes.

The crystalline nature of the tablet components used was confirmed in microscope investigations. For SEM photographs we used particles of MCC and of specially crystallized allapinin, which had elongated and hexagonal shapes, respectively. The allapinin retained its form even in the tableted products, although the dimensions of the crystals had diminished considerably. The granular type of structure of the tablets was retained, on the whole, when MCC was added. Moreover, a fairly uniform distribution of MCC in the preparations was observed.

The electron-microscope investigations showed the presence in the dispersed preparations of, together with the granular formations of the initial drug, elongated crystallites witnessing the presence of MCC. Replicas from the surface and from cleavage faces of the tablets showed well-defined fairly large crystals of allapinin, frequently covered with globular formations. On the addition of MCC, elongated layers of fibrillar nature appeared corresponding in structure to cellulose, which has some affinity with the drug, and this explains the increased strength of tablets with added MCC. At the same time, the dimensions of the crystals had substantially diminished, which correlates with the x-ray diffraction investigations.

With the aim of improving the capacity of the tableted agents for prolonged action, we used methods of mechanodestruction.

Fig. 7. ESR spectra of samples of MCC before (*1*) and after micronization for 30 min at 20 (*2*), 40 (*3*), and 60 g (*4*).

We studied structural features of MCC subjected to breakdown as a function of the time of treatment (Figs. 4 and 5). Thus, for the initial MCC in the optical microscope we observed anisodiametric particles consisting of fragments of fibers, with intense luminescence in polarized light, which showed a high degree of crystallinity. After micronization under severe conditions (30 min at 20, 40, and 60 g), the structure of the MCC had changed significantly; the anisodiametricity had disappeared and very small shapeless particles had arisen that also possessed luminescence in polarized light the degree of which decreased with an increase in the intensity of breakdown, showing a fall in crystallinity during such treatment. While the mean dimensions of the initial MCC were 100 μm, after 30 minutes micronization at 20 g they were 19 μm; at 40 g, 13 μm; and at 60 g, 8 μm — i.e, they had diminished by an order of magnitude.

SEM investigations showed that, on grinding, the particles of MCC had lost their elongated acicular form and became smoother, structureless, and rounded, which presupposes a smaller degree of irritation on the use of the drug preparations. The surface of the tablets with the addition of micronized MCC became finely granular and more homogeneous. And while when MCC that had been ground for 30 min at 20 g was used it was sometimes possible to distinguish these particles in the surface of the tablets, with an increase in the load (40 and 60 g) no MCC could be seen, which showed a further homogenization of the preparation and an increase in the possibility of an interaction between the components.

Analysis of diffractograms (Figs. 1 and 2) showed that the degrees of crystallinity for MCC and drugs decreased in proportion to an increase in the time of treatment and in the energy of loading, leading to amorphization under severe conditions. While for the initial MCC the DC amounted to 78-80%, after 30 minutes micronization at 20, 40, and 60 g it amounted to 54, 52, and 51%, respectively. At the same time, while at 20 g it retained all the four peaks characteristic for cellulose-1, at 40 and 60 g a single very diffuse maximum at 22.6° remained, showing the pronounced amorphization of the MCC. The same thing was observed for the mixtures of MCC with drugs treated under the same conditions. For MCC with allapinin at 20 g weak crystallinity peaks were still observed for both substances (DC_{MCC} = 42.5%), while at 40 and 60 g both substances underwent practically complete amorphization.

It must be mentioned that radicals appeared only in samples subjected to micronization under severe conditions. Figure 7 shows ESR spectra of the paramagnetic centers (PMCs) of such samples, consisting of a weak singlet signal with a g-factor and a width ΔH = 10 G. A correlation can be seen between the intensity of the signal (concentration of PMCs) and the degree of mechanical effect: the more severe the micronization conditions, the greater the number of long-lived radicals that appeared; however, these disappeared in the course of one year.

The possibility of using MCC in the production of tableted compositions based on allapinin has been determined. Figures 8 and 9 give the results of a determination of the kinetics of the release of allapinin from model systems and from tableted drug compositions. A prolongation effect on the addition of MCC is observed, which is the more pronounced the greater the degree of grinding. The nature of the liberation of allapinin from tablets with MCC (instead of the 35 min for the control, 1-2 h for the tablets with MCC) shows the promising nature of its use in the production of drug compositions with retarded release of the active principle.

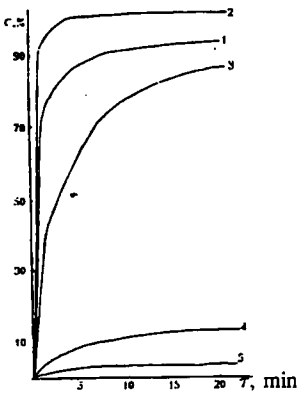

Fig. 8

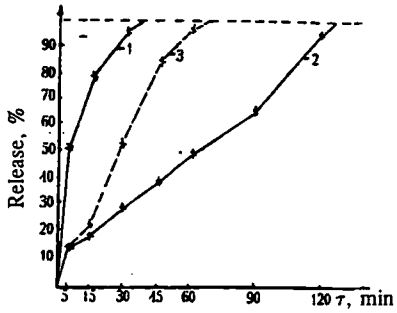

Fig. 9

Fig. 8. Solubility curves: *1*) allapinin, init.; *2*) after micronization (10 min, 60 g); *3*) mixture of allapinin with MCC (1:1) after micronization (10 min, 60 g); *4*) (30 min, 40 g); *5*) (30 min, 60 g).

Fig. 9. Kinetics of the release of allapinin from tablets: *1*) control; *2*) tablet with MCC (500 μm); 3) tablet with MCC (80 μm).

EXPERIMENTAL

X-ray diffraction studies [6] were conducted on a DRON-3M diffractometer with monochromatized CuK_α radiation at a voltage of 20-28 kV and a current strength of 15-18 mA, these values being chosen to suit the preparation under investigation. The samples were prepared by molding the ground preparation in the form of tablets. Recording was made in the interval 2θ = 10-30°.

IR spectra were taken on a Specord 75IR spectrometer. Tablets were prepared by molding the ground samples with KBr [4].

Microscope studies were made with MBI-6 and MBS-1 optical microscopes, which enabled us to determine the external form, shape, and dimensions of the samples and also the presence of pores, defects, and degrees of swelling and also the homogeneity of the samples. To investigate the supermolecular structure of the surface of the samples we used the method of two-stage polystyrene-carbon replicas [7] shadowed with Pt.

Shadowing was carried out in a VUP-4K vacuum apparatus. The replicas were viewed in a SEM-100 electron microscope. For the electron-microscope studies under scanning conditions the samples were sputtered with silver and were then examined in a SEM-200. To detect free macroradicals we used a Bruker ER 200 DSRC ESR spectrometer [8].

The MCC was obtained by the acid hydrolysis of cotton cellulose in 3% HNO_3 at 100°C for 3 h and was subjected to micronization in a Gefest (St. Petersburg) AGO-2 planetary-centrifugal grinder-activator at various levels of the load energy of grinding and for various times (5-30 min). Samples of MCC and of allapinin were subjected to grinding both separately and as a mixture (1:1).

The solubility of the preparations was analyzed in an instrument of the type with a rotating basket [9] in which the sample under investigation (weighing 0.01-0.05 g) was placed. The basket was rotated in the solvent (0.1 N HCl, V = 900 ml) at the rate of 100 rpm. Samples of the solution were taken after predetermined intervals of time and were filtered through a Blue Ribbon filter. The amount of active principle in the filtrate was determined spectroscopically on a SF-46 instrument at λ = 282 nm.

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