Effect of mechanical activation on the physicochemical properties of piroxicam with chitosan

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10.1070/MC2003v013n01ABEH001644

The mechanocomposites of piroxicam with chitosan exhibiting increased dissolution rate and solubility in comparison with the initial preparation were obtained.

The development of dispersed systems involving difficultly soluble medicines and auxiliary substances in order to solubilise medicines and to increase their biological availability became a common operation in pharmaceutical chemistry.[1,2] In the case of poorly soluble substrates and substrates melting with decomposition, mechanical activation is of special importance.[3–5] It was of interest to apply mechanical activation using low-soluble substrates to obtain compositions in which both components would pass into solution thus increasing the solubility of the medicine.

In this work, the natural polymer chitosan was chosen as a substrate.[6–8] It was demonstrated for some medicines[9,10] that the rate of their release from compositions with chitosan obtained by mechanical activation is much higher than that for the initial preparations.

The aim of this work was to obtain chitosan compositions with the anti-inflammatory analgesic drug piroxicam using mechanical activation and to study the physical and chemical properties of the drug in the mixtures with chitosan.

Piroxicam [4-hydroxy-2-methyl-*N*-(2-pyridyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide] was synthesised according to the published procedure.[11,12] Chitosan was obtained from chitin of the *Gammarus* crayfish of Altay.[13]

The mechanical treatment of initial components and piroxicam mixtures with chitosan was carried out in an AGO-2 planetary centrifugal mill[14] with water-cooled drums (drums volume of 40 ml, ball diameter of 6 mm, substance-to-ball mass ratio of 1:30, load per ball of 20 g, treatment time of 15 min).

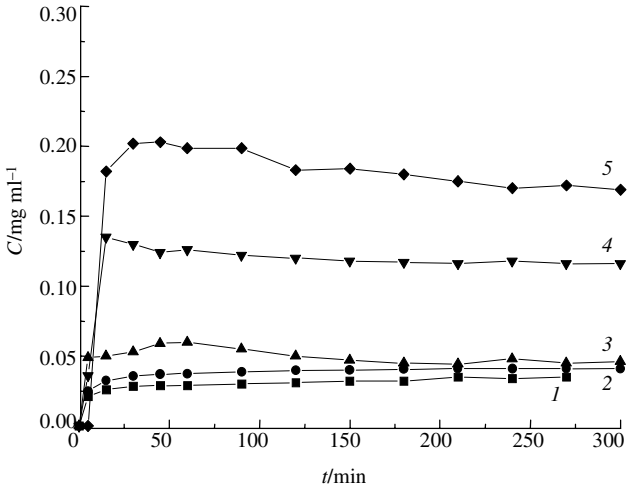

Figure 1 Dissolution curves of piroxicam–chitosan mixtures (1:1, by weight): (*1*) initial piroxicam, (*2*) physical mixture of components, (*3*) physical mixture of piroxicam with mechanically activated chitosan, (*4*) mechanically activated mixture, (*5*) physical mixture of mechanically activated components.

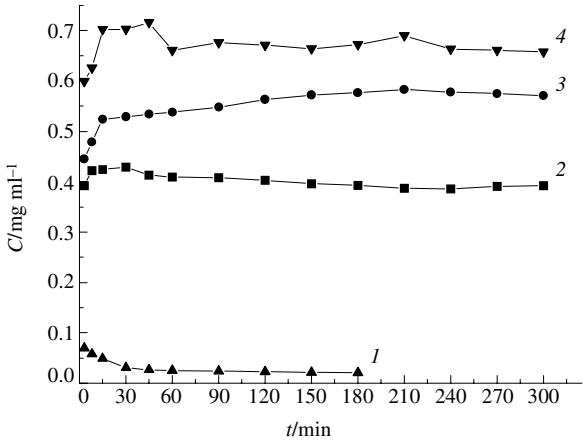

Figure 2 Dissolution curves of piroxicam–chitosan mixtures: (*1*) mechanically activated piroxicam, (*2*) mechanically activated mixture (1:3, by weight), (*3*) physical mixture of mechanically activated components (1:3, by weight), (*4*) mechanically activated mixture (1:10, by weight).

For comparison, physical mixtures were prepared by the simple mixing of initial components (as-obtained or mechanically activated) in the same ratios.

The X-ray diffraction analysis was conducted on a DRON-4 diffractometer using CuKα radiation. The IR spectra were recorded with a VECTOR-22 spectrophotometer (Bruker) in tablets with KBr.

The viscosimetry of chitosan was performed in an Ubbelode viscosimeter with a capillary diameter of 0.54 mm at 25 °C in a 0.2 M MeCOONa + 0.3 M MeCOOH buffer solution. Molecular masses were calculated using the equation[15] $[\eta] = 1.38\times10^{-4}Mr^{0.85}$.

The rate of release of the medicine was studied in a glass vessel thermostated at 37±0.5 °C containing 50 ml of water, and equipped with a mixer. The substance concentration in solution was determined with a Shimadzu UV-240 spectrophotometer at 358–365 nm. The chitosan concentration in solution was measured at 197 nm. The relative error of measurements was 0.5–0.8%.

According to the X-ray diffraction data and IR spectra, the initial piroxicam was a β-modification.[16–20]

In the mechanical treatment of both piroxicam and its mixtures with chitosan, we observed a colour change from white to yellow. After a 6 h exposure at 140 °C, as well as after storage for several months, the colour intensity of the mechanically activated piroxicam decreased. This colour change can be associated with the transition into the zwitterionic form.[21–23] The IR spectra of the mechanically activated sample exhibited a band at 3383 cm^{-1} within the region of stretching vibrations of NH and OH groups, which is characteristic of the α-modifica-

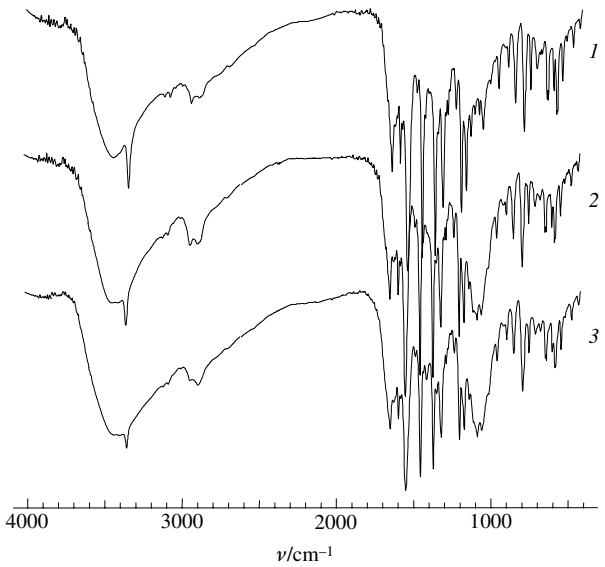

Figure 3 IR spectra of piroxicam–chitosan mixtures (1:3, by weight): (*1*) physical mixture of mechanically activated components, (*2*) mechanically activated mixture, (*3*) mixture of components isolated from solution.

tion and the monohydrate zwitterionic form of piroxicam.[16,17] The X-ray studies confirmed the absence of new reflections. Thus, other crystal phases did not appear during mechanical activation. At the same time, the broadening of diffraction peaks and a decrease in their intensity are indicative of the appearance of defects in the drug lattice and of its partial amorphization.

The initial chitosan had a weighed mean molecular mass of 1.6×10^6, which was reduced during mechanical treatment to 5×10^3 because of the mechanical cracking of macromolecular chains. The sample after mechanical treatment exhibited an insignificant solubility in water (0.65×10^{-2} mg ml^{-1}).

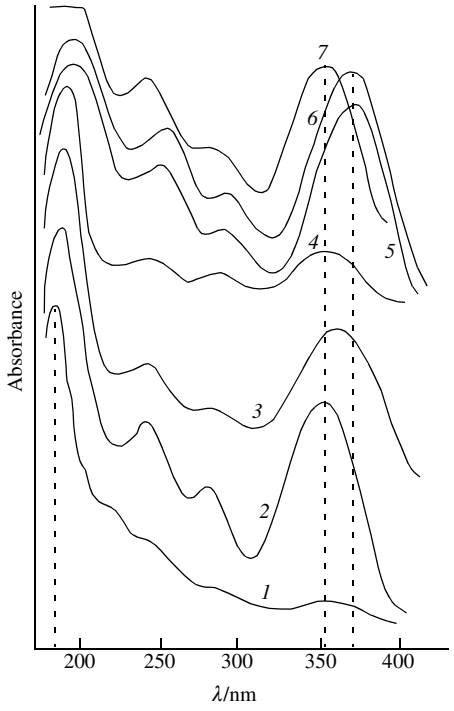

Figure 4 The absorption spectra of aqueous solutions of piroxicam and its mixtures with chitosan: (*1*) mechanically activated chitosan, (*2*) intact piroxicam, (*3*) mechanically activated piroxicam, (*4*) physical mixture of piroxicam with mechanically activated chitosan (1:3, by weight), (*5*) mechanically activated piroxicam–chitosan mixture (1:3, by weight), (*6*) physical mixture of mechanically activated components (1:3, by weight), (*7*) physical mixture of intact components (1:3, by weight).

Figures 1 and 2 show the kinetic curves of piroxicam release from the compositions with chitosan. The water solubility of piroxicam is ~0.015 mg ml^{-1}.[24] According to our data, the solubility of piroxicam in water at 37 °C is ~0.03 mg ml^{-1}. The dissolution rate and solubility of piroxicam in mechanically activated mixtures are higher than those for the initial and mechanically activated preparations.

The IR spectra of a mechanically activated mixture and a mixture of ingredients separately treated in a mill (Figure 3) exhibit differences in the regions of NH and OH stretching vibrations at 3450–3250 cm^{-1}. In the mechanically activated mixture, a broad band appeared in the region of the OH bending vibrations of chitosan at 1100–950 cm^{-1}. Vibration bands related to the S=O groups of piroxicam are in the same region.[16] The changes in the IR spectra are evidence for the interaction of piroxicam with chitosan, which likely results in the formation of hydrogen bonds between hydroxyl and amine groups of the biopolymer macromolecules and the functional groups of the drug. The formation of a molecular complex as a result of the joint mechanical activation of components can be responsible for changes in the dissolution rate of the drug and in its solubility.

An increase in the carrier concentration in the mixture (Figure 2) increased the rate of piroxicam release into solution. We assume that an excess of the carrier is necessary to provide the complete interaction of the drug with chitosan.

The highest dissolution rate and solubility were observed in the physical mixtures of mechanically activated components (Figures 1 and 2). An excess of the carrier also increased the concentration of the drug in solution (Figure 2).

Note that, if we mixed piroxicam with mechanically activated chitosan, we observe only an insignificant increase in the dissolution rate and solubility of the medicine (Figure 1, curve *3*). Similarly to the dissolution of a mixture of activated piroxicam with untreated chitosan, the solubility did not exceed that of the drug itself. Thus, neither activated piroxicam nor a mixture of chitosan with piroxicam subjected to mechanical activation (or mixtures in which only one of the components was activated) produced an effect similar to that observed in a mixture of mechanically treated components. We assume that the reason is the formation of water-soluble piroxicam complexes with chitosan. These complexes can be formed both in a reaction initiated by mechanical activation during the treatment of the mixture and during the dissolution of mechanically activated components in aqueous solution.

Mechanical activation of the components is a necessary condition for complex formation in solution, since the simple mixing of initial chitosan and piroxicam does not cause the solubilization of the medicine. The shifts of UV absorption bands (Figure 4) confirm the occurrence of interaction in the case when both components were mechanically treated, unlike the cases when only one of the components was treated. It is likely that the interaction in solution is promoted, on the one hand, by the transition of piroxicam into a metastable form exhibiting increased dissolution rate and solubility; on the other hand, a necessary condition is the cracking of biopolymer chains with the formation of low-molecular-weight products.

Judging from the band positions in the IR spectrum of the compound isolated from solution (Figure 3), the dissolution of a mixture of mechanically activated components results in the formation of the same molecular complex as that formed in the solid-phase interaction of chitosan and piroxicam initiated by mechanical treatment. However, the solubilization effect of the mixture activated mechanically is somewhat lower than that of a mixture of components activated separately. This is likely a consequence of the known effect of mutual damping.

Thus, we used mechanical activation for preparing piroxicam–chitosan compositions exhibiting increased dissolution rate and solubility of the medicine. The mechanical activation leads to the formation of a molecular complex of piroxicam with chitosan due to hydrogen bonds. The highest dissolution rate and solubility were exhibited by mixtures of separately activated components; their dissolution was accompanied by the formation of complexes in solution.

This work was supported by CRDF (grant no. REC–008), the Russian Foundation for Basic Research (grant no. 02-03-33299) and the Ministry of Education of the Russian Federation.

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Received: 18th July 2002; Com. 02/1970