# Mechanochemical Solubilization of Piroxicam with the Use of Microcrystalline Cellulose that Was Produced by Means of Catalytic Delignification of Sawdust of Aspen Wood

S. A. MYZ[1,2], T. P. SHAKHTSHNEIDER[1,2], A. S. MEDVEDEVA[3] V. V. BOLDYREV[1,2], S. A. KUZNETSOVA[4], B. N. KUZNETSOV[4], V. G. DANILOV[4] and O. V. YATSENKOVA[4]

[1]*Institute of Solid State Chemistry and Mechanochemistry, Siberian Branch of the Russian Academy of Sciences, Ul. Kutateladze 18, Novosibirsk 630128 (Russia)*

*E-mail: apenina@solid.nsc.ru*

[2]*Novosibirsk State University, Research and Education Centre for Molecular Design and Ecologically Safe Technologies, Ul. Pirogova 2, Novosibirsk 630090 (Russia)*

[3]*Favorsky Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, Ul. Favorskogo 1, Irkutsk 664033 (Russia)*

[4]*Institute of Chemistry and Chemical Technology, Siberian Branch of the Russian Academy of Sciences, Ul. K. Marksa 42, Krasnoyarsk 660049 (Russia)*

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## Abstract

An environmentally sound method to produce microcrystalline cellulose (MCC) has been developed. Conditions have been adjusted that make it possible to produce top-quality MCC with a good yield. The produced MCC is highly competitive with commercial samples in its performance. By means of combined mechanical activation of piroxicam and MCC that was obtained following a new technology, compositions have been prepared that offer higher than usual speed of dissolving of a medicinal substance. It has been demonstrated that "graft complexes" are formed between MCC and piroxicam as a result of interaction of the ingredients to form hydrogen bonds.

## INTRODUCTION

It is common knowledge that combined mechanical treatment of medicinal substances with auxiliary materials in activator-mills allows one to stabilise metastable states that emerge in mechanical activation of medicinal preparations, and it contributes to an increased rate of dissolving and to solubility of sparingly soluble medicinal substances, and to their enhanced biological availability [1, 2]. Microcrystalline cellulose (MCC), one of these auxiliary materials that is widely applied to produce compacted and powdered cosmetics, and as filler in the manufacture of medicinal forms. Chemical and physical stability of cellulose from MCC, an excellent compressibility of a tablet allow its use as auxiliary material when tableting finished medicinal forms.

Research has demonstrated that combined mechanical dispersion of medicinal substances with MCC results in their amorphisation, the speed of dissolving and bioavailability of medicinal preparations [3–8] rises. Accordingly, it has been found in work [5] that the solubility of amobarbital from solid dispersions that were prepared by combined mechanical grinding with MCC, increases by the factor of 6–8.

This paper studies the possibility of non-steroid anti-inflammatory preparation of piroxicam for solubilization by its combined mechanical treatment with MCC. A microcrystalline

cellulose that has been produced from sawdust following a new, environmentally sound technology we had developed was used as MCC.

## EXPERIMENTAL

The microcrystalline cellulose was obtained by means of catalytic delignification of sawdust of aspen wood in the Institute of Chemistry and Chemical Technology, Siberian Branch of the Russian Academy of Science (ICCT, SB RAS) [9]. The process that is of a two-stage nature was conducted in a reactor from stainless steel of capacity 200 $cm^3$ at a temperature of 100–130 °C, with the liquor ratio (LR) of 10–15 over the course of 1–2 h. 2 % $H_2SO_4$ solution was used as the catalyst at the stage of obtaining a fibrid; the final stage was performed without any catalyst. 4.2 % $H_2O_2$ solution and 25.8 % $CH_3COOH$ solution were used at both stages. The analysis of permolecular structure of the obtained MCC samples was conducted by X-ray diffraction analysis and IR spectroscopy.

The study used piroxicam that was synthesized in Irkutsk Iistitute of Chemistry, SB RAS, according to a developed original method [10, 11].

Mechanical treatment of piroxicam samples with MCC was conducted in an AGO-2 planetary centrifugal mill (Russia) with water-cooled barrels (capacity of the steel barrels of 40 mL, the diameter of balls of 6 mm, the load per ball of 20*g*, the ratio of mass of samples to the mass of balls comprised 1 : 30, the treatment time was 15–30 min) and in a SPEX 8000 vibrating mill (the USA) (a steel barrel of capacity 60 mL, the diameter of balls of 6 mm, the ratio of mass of weighted sample to the mass of the balls load was equal to 1 : 20, the load per ball of 10*g*, the treatment time was 30 min). The mass ratio of ingredients in the piroxicam/MCC mixtures was 1 : 1, 1 : 3, and 1 : 10.

The speed of release of a medicinal substance was examined as follows. A weighted sample that contained an excess of piroxicam was put in a (37±0.5) °C thermostated glass beaker that was equipped with a mechanical stirrer and that contained 100 mL of water. The solution was taken after certain time slices using pipette batcher and filtered off. The concentration of substance in the solution was determined by measuring the optical density of the analysed solution in the region of 358–365 nm in a Shimadzu UV-240 spectrophotometer (Japan).

X-ray diffraction analysis of powder samples was conducted with the use of D8 DISCOVER diffractometer (Bruker), Cu$K_\alpha$ radiation.

IR spectra were recorded in an Infralyum FT-801 Fourier transform spectrophotometer (Russia) in tablets with KBr (4 mg of an investigated sample were mixed with 500 mg of dry KBr).

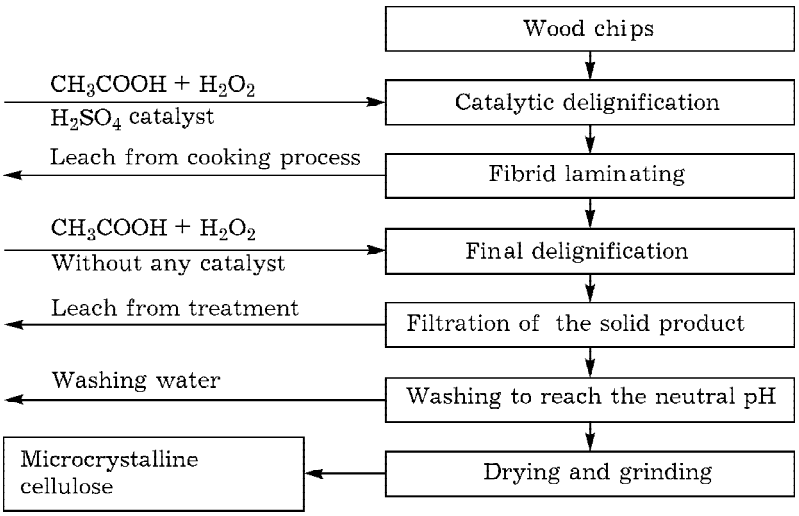


Fig. 1. Schematic diagram to produce microcrystalline cellulose from wood waste.

TABLE 1

Effect of delignification conditions on the yield and polymerization degree of microcrystalline cellulose (MCC) from aspen wood sawdust

| Stage of delignification | | | | | | Yield of MCC | MCC polymerisation degree |
|---|---|---|---|---|---|---|---|
| Catalytic | | | Final | | | | |
| $T$, °C | LR | τ, h | $T$, °C | LR | τ, h | | |
| 120 | 12 | 2.0 | 120 | 15 | 2.0 | 90.9/30.5 | 127 |
| 120 | 15 | 2.0 | 120 | 15 | 1.0 | 94.3/32.2 | 217 |
| 130 | 15 | 2.0 | 100 | 15 | 1.0 | 76.9/31.7 | 218 |

*Notes*. 1. The first value is the yield of MCC that was calculated for theoretically dry fibrid; the second one, for theoretically dry wood. 2. LR – the liquor ratio.

## RESULTS AND DISCUSSION

Applied technologies to produce MCC from wood are based on the application of traditional methods of obtaining cellulose and on the subsequent processes of its mechanical grind, acid or alkaline hydrolysis treatment, filtration, washing, and drying. These technologies are of many-stage and power-consuming nature, while the application of compounds of sulphur, chlorine, and inorganic acids as the reagents makes the production ecologically dangerous. In this relation, improvement of the processes to produce MCC is urgent.

An environmentally sound method of producing MCC that was developed in the ICCT, SB RAS, includes a stage of obtaining a fibrid with a low content of residual lignin, catalytic delignification of sawdust by a mixture of acetic acid and hydrogen peroxide in the presence of 2 % $H_2SO_4$ solution, and the final delignification by the mixture of acetic acid and hydrogen peroxide without any catalyst (Fig. 1). The adjusted conditions to carry out the both stages make it possible to obtain a top-quality fibrid after the stage of catalytic delignification and MCC with a good yield after the final delignification from sawdust of various wood species [12–17]. Table 1 gives data for the influence of conditions of performing the catalytic and final delignification stages on the MCC yield and on its polymerisation degree.

From the diffractogram that is presented in Fig. 2 it can be seen that the crystal lattice of MCC that has been obtained of aspen sawdust is identical to the monoclinic lattice of cellulose I [18]. The crystallinity index for MCC samples from aspen sawdust (0.74) that was calculated from X-ray diffraction data is comparable to that for commercial MCC samples (0.64–0.80 [19–21]) (Table 2).

X-ray phase investigations of mechanically processed mixtures of piroxicam with MCC that was produced following the new way (Fig. 3)

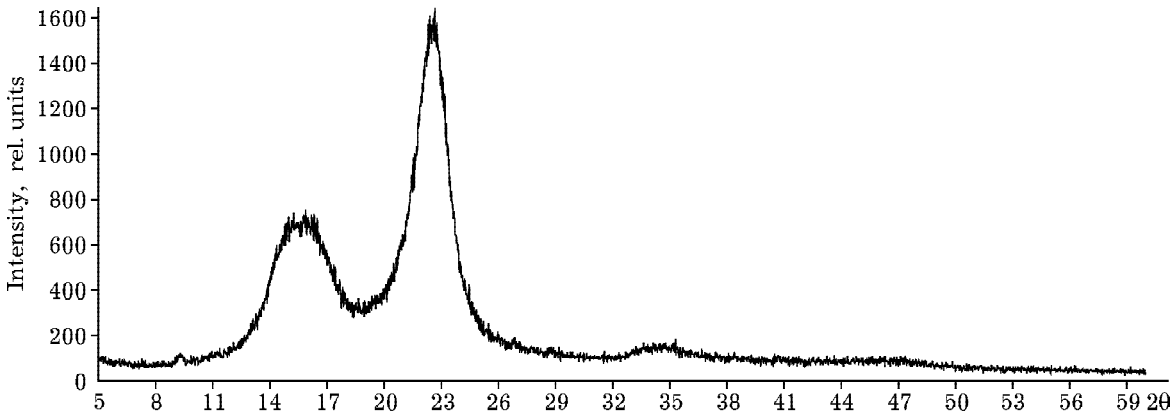


Fig. 2. Diffractogram of microcrystalline cellulose that has been produced from aspen wood.

TABLE 2

Sizes of crystallites and crystallinity indexes for microcrystalline cellulose (MCC)

| MCC sample | Size of crystallites along the normal line to the plane (002), Å | Crystallinity index |
|---|---|---|
| MCC from aspen sawdust | 35.28 | 0.74 |
| MCC from cotton linter [20] | 58.00 | 0.80 |
| MCC from commercial sulphate pulp [20] | 45.00 | 0.65 |
| MCC from commercial sulphite cellulose [20] | 40.00 | 0.67 |
| MCC from the hydrolytic lignin [21] | 38.6–40.5 | 0.62–0.64 |
| MCC Avicel PH 102 [22] | 46.3 | 0.64 |

have demonstrated that mechanical treatment leads to partial amorphization of a medicinal substance, and with an increased quantity of MCC and the time for treatment, it leads to the formation of X-ray amorphous samples. The absence of reflexes from the diffractograms testifies that grinding of the formulation constituents, disordering of their crystal structure, and the formation of nanocrystal or amorphous composites occurs as a result of the mechanical treatment.

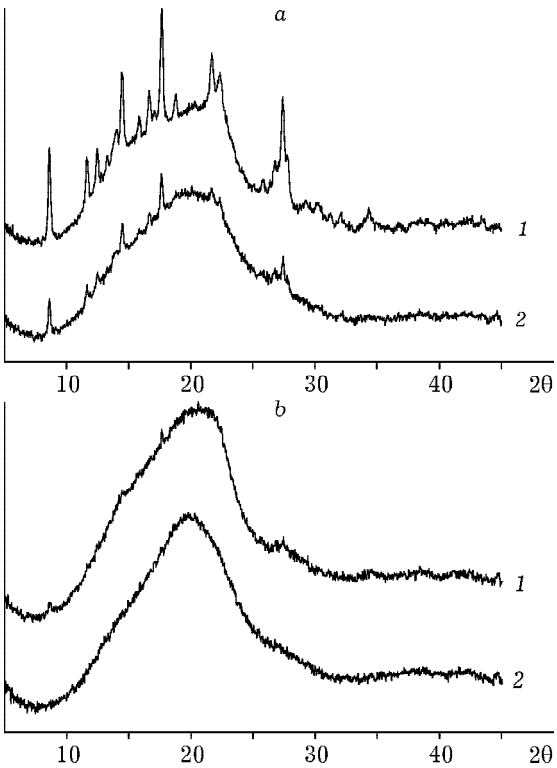


Fig. 3. Diffractograms of piroxicam mixtures with MCC with the mass ratio of 1 : 3 (*a*) and 1 : 10 (*b*) that were mechanically activated in AGO-2 mill over the course of 15 (*1*) and 30 min (*2*).

Figure 4 presents dissolving curves of pure piroxicam and of that mixed with MCC. It is evident that mechanical treatment of piroxicam with MCC leads to an increase in the dissolving speed of a medicinal substance irrespective of the type of the applied mill: that of vibrating (see Fig. 4, *a*) or of more energy-intensive centrifugal planetary nature (see Fig. 4, *b*). At the initial point in time, supersaturated water solutions of piroxicam are formed, and then the concentration of the medicinal substance drops down to reach an equilibrium value.

These dissolving curves are typical for metastable systems that were obtained from mechanical activation. Accordingly, mechanically processed mixtures of several medicinal substances (benzene carboxylic acid, aspirin, salicylic acid, Levomycetinum, Diazepamum) with MCC in papers of Nakai *et al.* [4] exhibited high speeds of excretion of medicinal substances to form supersaturated solutions. The results arrived at allowed the authors to make an inference that medicinal substances under mechanical treatment with MCC are dispersed within a matrix in the form of molecules or molecular microensembles. It was found by IR spectroscopic studies [22] that molecules of medicinal substances in mechanically processed mixtures are described in terms of monomolecular distribution and they are connected with hydroxyl groups of cellulose by hydrogen bonds. The mechanism to release substances in this case is assumed to be different from conventional dissolving mechanism. While only the molecules that are located on a surface of the solid body may diffuse into the solution in the course of usual dissolving, water weakens hydrogen bonds between MCC

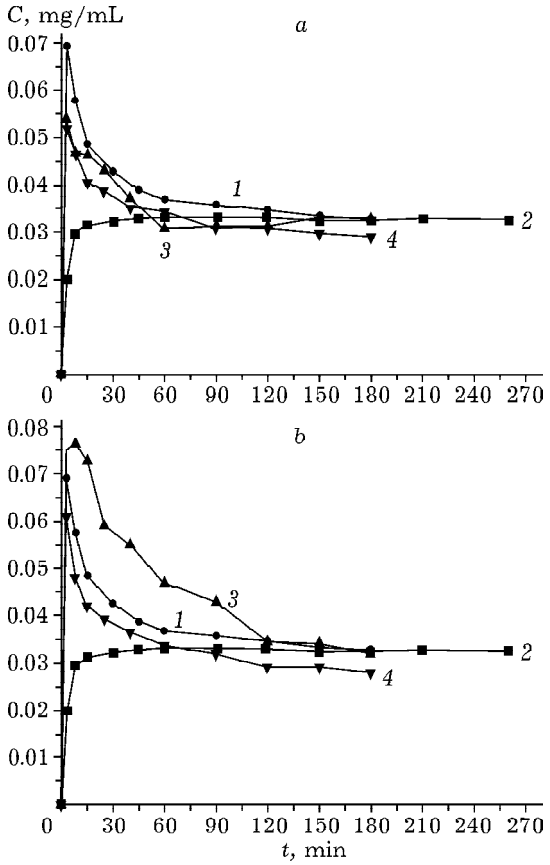


Fig. 4. Dissolving curves of piroxicam and its mixtures with MCC that have been activated in mills AGO-2 (*a*) and SPEX 8000 (*b*): *1*, *2* – mechanically activated (*1*) and source piroxicam (*2*), *3*, *4* – piroxicam/MCC mixture with the ratio 1 : 1 (*3*) and 1 : 10 (*4*).

molecules in the case of mechanically processed mixtures and makes easier the release of molecules of medicinal substances from the matrix.

An assumption can be made that mechanical treatment of piroxicam with MCC leads to dispergation of a medicinal substance and to its distribution within the carrier matrix.

In its turn, the formation of nanocrystal or amorphous composites (as witnessed by the absence of reflexes from X-ray diffractograms) involves a gain in specific surface of piroxicam and an increase in the speed of its release into the solution. It seems likely that the higher than usual dissolving speed of mechanically activated piroxicam is also determined by its amorphization and transformation into zwitterionic form, which was evidenced previously for piroxicam in its mechanical treatment with poly(vinylpirrolidone) [23, 24]. Yellow colouring of the obtained samples with MCC testifies supposedly that the zwitterionic form of a medicinal substance is also formed in the course of mechanical treatment of piroxicam with MCC.

Changes in the region of stretching vibrations of NH and OH groups of a medicinal substance are present in IR spectra of mechanically activated mixtures of piroxicam with MCC (Fig. 5), which bears witness to the interaction of the ingredients during the mechanical activation. It appears that these changes are related to the formation of hydrogen bonds between the ingredients that involve functional groups of piroxicam and OH groups of MCC. The resulting is that "graft complexes" are formed that show a higher than usual dissolving speed of a medicinal substance. The formation of such complexes was previously evidenced for Clophelinum, a medicinal substance that contains amino groups, in the course of its mechanical treatment with MCC in a planetary centrifugal mill [7].

Upon the dissolving of mechanically activated pure piroxicam, its concentration in the solution did not exceed or slightly exceeded the concentration of the medicinal substance in the case of dissolving of mechanically activated mixtures. However, samples with MCC, unlike a pure medicinal substance, are more stable and piroxicam is preserved in the active form for a long time owing to the formation of hydrogen bonds between the ingredients (see Fig. 4, *a*, curve *4*).

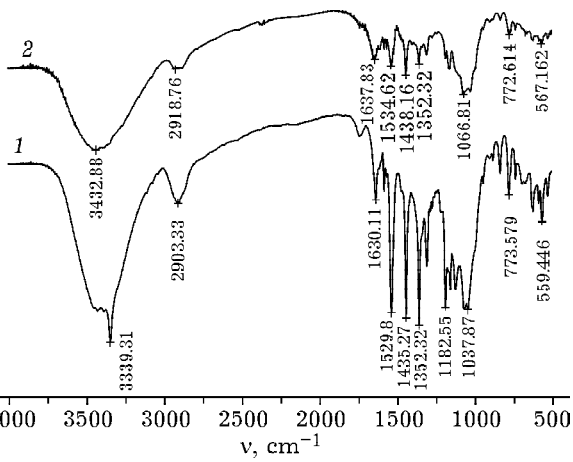


Fig. 5. IR-spectra of piroxicam mixtures with MCC (1 : 3): *1* – physical mixture of mechanically activated ingredients, *2* – mechanically activated mixture.

## CONCLUSION

Thus, it has been demonstrated using piroxicam as an example that MCC that has been produced from sawdust following a new technology can be used to solve the problem of solubilization of medicinal substances and as an auxiliary material in pharmacy.

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