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# THERMOANALYTICAL INVESTIGATION OF DRUG–EXCIPIENT INTERACTION
## Part II. Activated mixtures of piroxicam with cellulose and chitosan

*V. A. Drebushchak*[1,2*], *Tatyana P. Shakhtshneider*[1,3], *Svetlana A. Apenina*[1,3], *Alevtina S. Medvedeva*[4], *Líubov' P. Safronova*[4] *and V. V. Boldyrev*[1,3]

[1]Novosibirsk State University, 'Molecular Design and Ecologically Safe Technologies' REC-008, Ul. Pirogova 2 Novosibirsk 630090, Russia
[2]Institute of Mineralogy and Petrography SB RAS, Pr. Ac. Koptyuga 3, Novosibirsk 630090, Russia
[3]Institute of Solid State Chemistry and Mechanochemistry SB RAS, Ul. Kutateladze 3, Novosibirsk 630128, Russia
[4]A. E. Favorsky Irkutsk Institute of Chemistry, SB RAS, Ul. Favorskogo, 1, Irkutsk 664033, Russia

Piroxicam–excipient (chitosan or cellulose) mixtures after mechanical activation were investigated using DSC. Crystallization of amorphous piroxicam was detected near 80°C in the mixtures of the components activated separately. If the components in the mixture are activated together, amorphous piroxicam does not crystallize at heating.

Both excipients interact with piroxicam, decreasing its melting point and enthalpy of melting. Mechanical activation intensifies the interaction, decreasing the melting point by 8°C and reducing the enthalpy of melting two times.

Both excipients interact identically with piroxicam, affecting identically its melting parameters. Nevertheless, the two excipients affect its solubility in water very differently. Cellulose does not change the solubility, but chitosan increases it ten times. The mechanism of piroxicam dissolution from the mixture with an excipient is discussed.

***Keywords:*** *cellulose, chitosan, drug-excipient interaction, DSC, melting, piroxicam, solubility*

## Introduction

Information on the interaction between the drug and excipient is very important when new drug formulations are developed [1, 2]. The interaction governs the principle compatibility of the drug with excipients, affecting the biological activity and shelf life of a drug formulation. Thermal analysis is quite fast and accurate technique, allowing one to receive the information about the changes in the thermal properties of components in a drug dosage form, but unfortunately the reliable relations between the changes in thermal properties and the parameters of a drug interesting for pharmacologists are not recognized so far [3–6].

Piroxicam is a non-steroidal anti-inflammatory drug, with low solubility in water. Review of the references describing its properties is in previous report [7]. To increase its bioavailability and therapeutical activity, one should develop the drug formulation with increasing solubility. It was shown that the solubility of piroxicam increases after mechanical activation in a mixture with chitosan but remains unchanged with cellulose [8, 9].

Mechanical activation of a drug leads to the partial amorphization of its crystalline structure, increasing, in turn, its chemical reactivity [10].

The objective of this work was to investigate thermal properties of piroxicam-excipient (cellulose and chitosan) mixtures, untreated and mechanically activated. The results of the measurements are to be used for the optimization of drug formulation. This report is the second part of the investigations. In the first part we reported the results of the investigations of untreated pure starting materials.

## Experimental

### *Samples*

Starting materials (microcrystalline cellulose, chitosan, and piroxicam) were described in detail in the previous report [7]. All samples were investigated air dry. The combinations of piroxicam–excipient mixtures together with pure components are listed in Table 1. 'Activated' samples were treated in a ball-mill, 'activated+untreated' means that piroxicam was activated and then mixed with untreated excipient, 'activated separately' means that piroxicam and excipient were activated each in a pure form and then mixed together, 'activated together' means that untreated piroxicam was mixed with untreated

* Author for correspondence: dva@uiggm.nsc.ru

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*Akadémiai Kiadó, Budapest, Hungary*
*Springer, Dordrecht, The Netherlands*

**Table 1** Experimental conditions of DSC measurements. Type I: from 30 to 220°C at a heating rate of 9°C $min^{-1}$; type II: from 170 to 210°C at a heating rate of 2°C $min^{-1}$

| | Mass/mg | Type |
|---|---|---|
| | cellulose | |
| untreated | 1.76 | I |
| untreated | 14.27 | II |
| activated | 1.76 | I |
| activated | 13.75 | II |
| | chitosan | |
| untreated | 1.56 | I |
| untreated | 13.50 | II |
| activated | 1.60 | I |
| activated | 13.87 | II |
| | piroxicam | |
| untreated | 1.81 | I |
| untreated | 1.55 | I |
| untreated | 13.74 | II |
| activated | 1.67 | I |
| activated | 1.65 | I |
| activated | 13.82 | II |
| | piroxicam+chitosan | |
| untreated both | 1.62 | I |
| untreated both | 13.63 | II |
| activated+untreated | 1.61 | I |
| activated+untreated | 13.45 | II |
| activated+untreated | 13.46 | II |
| activated separately | 1.68 | I |
| activated separately | 13.87 | II |
| activated together | 1.72 | I |
| activated together | 13.43 | II |
| | piroxicam+cellulose | |
| untreated both | 1.62 | I |
| untreated both | 13.47 | II |
| activated+untreated | 1.63 | I |
| activated+untreated | 13.86 | II |
| untreated+untreated | 13.54 | II |
| activated separately | 1.64 | I |
| activated separately | 13.57 | II |
| activated separately | 13.45 | II |
| activated together | 1.56 | I |
| activated together | 13.50 | II |

excipient and then the mixture was activated in a planetary ball mill. The components were mixed in the ratio 1:3 by mass.

Several samples (for example, 'activated' piroxicam of 1.67 and 1.65 mg or 'activated+untreated' mixture of piroxicam+chitosan of 13.45 and 13.46 mg) were measured twice. These experiments were carried out for checking the reproducibility of the results. The repetitions were performed two weeks after the first measurements and with freshly prepared (activated) samples.

*Methods*

Mechanical activation of the samples was performed using planetary ball mill AGO-2 with water-cooled drums (volume of the steal drums 40 mL; steal balls 6 mm in diameter; acceleration 20 g). The parameters of the sample treatment were as follows: the mass ratio sample-to-balls of 1:30 and the duration of 15 min.

Calorimetric measurements were carried out using DSC-204 (Netzsch) with a standard aluminum crucible of 40 mL in an atmosphere of dry argon (25 mL $min^{-1}$), calibrated according to the procedure described in [11]. Two types of the experiments were performed. In the first type, samples with a mass of about 1.5 mg were heated from 30 to 220°C at a heating rate of 9°C $min^{-1}$. These measurements provided us with the information about the dehydration of excipients, crystallization of amorphous piroxicam after the activation, and its melting near 200°C. In the second type of the measurements, samples with a mass of about 13.6 mg were heated from 170 to 210°C at a heating rate of 2°C $min^{-1}$. These experiments provided us with accurate data on the melting of piroxicam in the mixtures.

The rate of the release of piroxicam from a mixture was investigated by placing a weighed portion of a sample, containing the drug in excess, into a glass vessel with 100 mL of water, equipped with a mixer, with the temperature control at 37±0.5°C. The concentration of the substance in solution was determined with a Shimadzu UV-240 spectrophotometer after specified time intervals. The intensity of the band at 358 nm was measured. Relative error of the measured values was 0.5–0.8%.

## Results

*Mechanical activation of pure substances*

DSC results of chitosan after mechanical activation are shown in Fig. 1, together with those for the untreated chitosan. Kinetics of dehydration changes

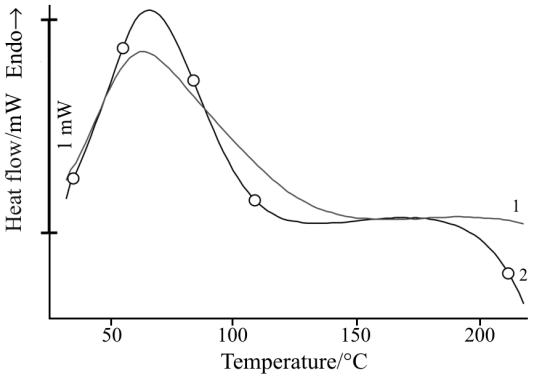


**Fig. 1** DSC results of chitosan 1 – before and 2 – after mechanical activation. Thermal stability of chitosan decreases significantly after the treatment: exothermic effect above 175°C is much greater than that in untreated sample

slightly, it is seen from the changes in the broad peak below 120°C. The peak becomes slightly higher and more narrow than that of untreated sample. More significant are the changes in thermal stability of chitosan. Exothermic effect above 180°C is much greater as compared to that in the untreated sample, thermal decomposition is much rapid.

DSC results for activated and untreated cellulose are shown in Fig. 2. Water content increases significantly and becomes close to that in chitosan. Amplitude of the dehydration peak after the activation is nearly 1 mW, like that in Fig. 1. Thermal stability of cellulose after mechanical activation decreases similarly to chitosan. DSC signal at high temperature declines downwards indicating the exothermic effect, but the value of the signal is much less than that for chitosan. Thermal stability of activated cellulose is greater than that of activated chitosan.

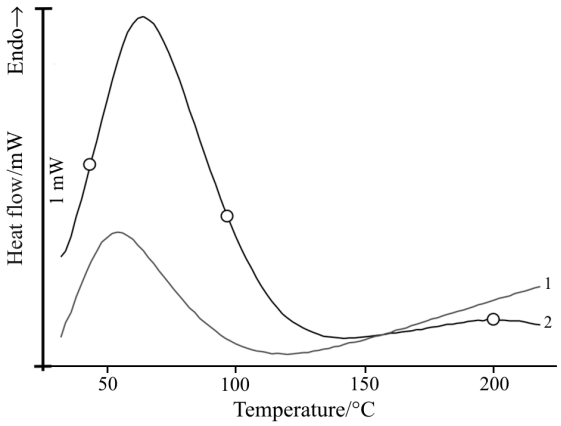


**Fig. 2** DSC results of cellulose 1 – before and 2 – after mechanical activation. Water content of the sample increases significantly and becomes nearly equal to that in chitosan (compare the peak amplitude with that in Fig. 1). Thermal stability of cellulose after the treatment decreases, yielding an exothermic effect above 200°C

Mechanical activation changes the thermal properties of piroxicam both near room temperature and close to the melting point. Low-temperature part of DSC results for piroxicam, untreated and activated, are shown in Fig. 3. Exothermic peak near 80°C is considered conventionally as the crystallization of amorphous part of the sample after mechanical activation, i.e., after the destruction of the crystal structure. Enthalpy of the crystallization is about 9% of the enthalpy of melting [7].

Melting of two samples, untreated and activated, is shown in Fig. 4. Two main results of the mechanical activation of piroxicam are evident from the figure: (1) the melting point is depressed and (2) the process itself is not equilibrium. The whole melting peak of activated piroxicam is shifted to the

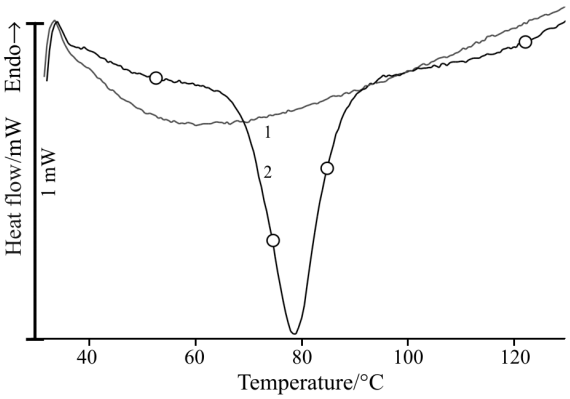


**Fig. 3** Near-room-temperature part of DSC results for piroxicam 1 – before and 2 – after mechanical activation. Exothermic peak near 80°C is the crystallization of an amorphous phase that was formed during the activation

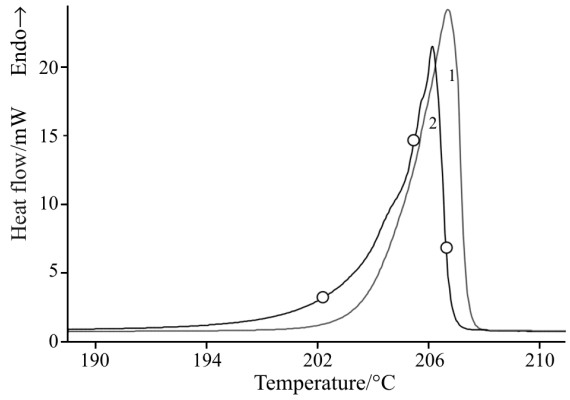


**Fig. 4** Melting of piroxicam 1 – before and 2 – after mechanical activation. The treatment produces the defects in crystalline structure of piroxicam, decreasing its melting point and making DSC signal wavy due to the inhomogeneity of the sample

left as compared to the peak of untreated sample. The rising part (left) of the peak is wavy. In trying to calculate the onset point, we face the problem of extrapolation of the 'isothermal' increase in the signal to a straight line extrapolating the baseline. Most likely, this is the result of inhomogeneity in the treated sample. As a sample in the ball mill is 'activated' only at the points of a strike between balls and walls, one should not be surprised that different parts of a powder are activated nonuniformly. The activation produces the defects in the crystal structure of particles and makes them amorphous partly, which manifests itself in the exothermic 'crystallization' at heating (Fig. 3). Simultaneously, the movement of the balls stirs the powder and decreases the inhomogeneity, but not completely. The depression of the melting point depends on the degree of activation,

and non-uniformly activated powder has a temperature range where the different portions of a sample melt, not a single melting point. Such a melting is not isothermal in fact. This consideration is valid only for nonequilibrium conditions of scanning heating, for the defects in the crystal structure of a sample can be annealed at low heating. Anyway, the depression of the melting point characterizes the changes in a sample and its degree of activation after mechanical treatment in a ball mill, but one should not pay too much attention to the exact value of the depression.

*Dehydration and crystallization in mixtures*

DSC results for the mixtures of untreated piroxicam and excipients (cellulose and chitosan) below 150°C are the superposition of those for pure substances [7]. Similarly, the results for activated piroxicam and excipients, untreated or activated separately, are the superposition of the results from individual components in a mixture. For example, pure activated piroxicam has the exothermic peak of crystallization near 80°C, and pure activated cellulose has the endothermic peak of dehydration (enlarged as compared to untreated cellulose) near 60°C. Mixture of piroxicam and cellulose, activated separately, has the enlarged endothermic peak near 60°C with an exothermic component near 80°C (line 3 in Fig. 5). The amplitude of the exothermic contribution is equivalent to that of pure activated piroxicam. For the activated mixtures of piroxicam and excipients (i.e., first mixed and then activated), the results are different. There are no traces of exothermic crystallization on line 4 in Fig. 5, but piroxicam in this sample is mainly amorphous, because its X-ray powder diffraction pattern contains weak and broad reflections of crystalline piroxicam and enthalpy of melting is 2 times less than for piroxicam in the untreated mixture ('Discussion').

*Melting*

The measurements of piroxicam melting (experiments of type II) provide us with the results on 1) melting point; 2) enthalpy of melting; and 3) the changes in the baseline (heat capacity) before and after the melting. It was shown above that the evaluation of the melting point ('onset' point) becomes ambiguous for the activated piroxicam (Fig. 4). Sometimes, we have had to perform the 'manual' evaluation, for the Netzsch Proteus software failed to found out the onset point itself in an automatic mode. Different ways of the evaluations of the same measuring curve range by as much as 0.5°C. Similarly, the enthalpy of melting was found to range within the limits of about 5%. It is greater than the experimental errors (about 2%). We also faced the problem of choosing between manual and automatic evaluations of the enthalpy of melting, because sometimes tangential baseline was not appropriate for the evaluations. Anyway, the results of the evaluations are listed in Table 2, allowing us to realize what are the effects of piroxicam–excipient interactions.

Significant changes in a DSC signal arising after various ways of the treatment of piroxicam–excipient mixtures create many problems in the correct (unambiguous) evaluation of melting parameters ($T_m$ and $\Delta_m H$), but provide us with very informative

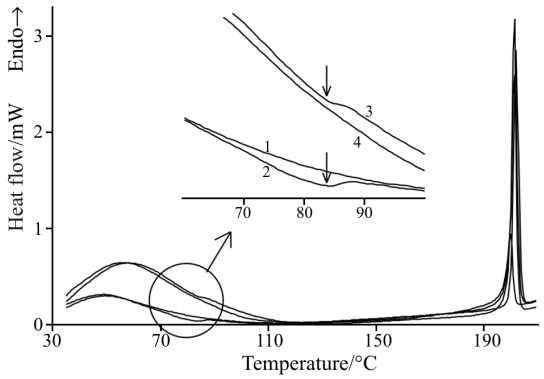


**Fig. 5** DSC results of piroxicam–cellulose mixtures: 1 – the physical mixture of untreated components, 2 – only piroxicam in the mixture was activated, 3 – the components in the mixture were activated separately, 4 – the mixture was activated as a single whole. The insert shows the temperature range where the amorphous part of piroxicam crystallizes. The arrows indicate the exothermic contribution from the crystallization

**Table 2** Parameters of piroxicam melting in the mixtures with excipients ($T_0$ is the onset temperature, $\Delta_m H$ is the enthalpy of melting)

| | $T_0$/°C | $\Delta_m H$/J g$^{-1}$ | $T_0$/°C | $\Delta_m H$/J g$^{-1}$ |
|---|---|---|---|---|
| | | pure piroxicam | | |
| untreated | 200.4 | 103 | 200.4 | 103 |
| activated | 199.8 | 99 | 199.8 | 99 |
| | with chitosan | | with cellulose | |
| untreated both | 198.3 | 98 | 199.3 | 92 |
| activated+untreated | 196.8 | 88 | 197.0 | 90 |
| activated separately | 196.3 | 96 | 198.2 | 96 |
| activated together | 192.8 | 56 | 192.1 | 40 |

indication of which factor is responsible for a particular property. Figures with a row DSC signal will be discussed below in detail.

## Discussion

*Effects of the drug–excipient interaction in the DSC results*

Excipients affecting the melting of piroxicam

The starting point of the investigations of drug–excipient interaction is the fact that the drug formulations usually differ from pure drug substances in biological activity and shelf life. It is conventional to consider the difference as the result of drug–excipient interaction, no matter what is the mechanism of the interaction [12–16]. Thermoanalytical results are very sensitive to any changes in the quality of the sample under investigation. In recent years several works were reported where TA experiments were used for the detection of the differences between the results of TG or DSC measurements of pure drugs and their mixtures with various excipients [17–21]. If the difference is detected, the drug-excipient interaction is concluded to exist. Here, we apply this concept to our results on DSC investigations of piroxicam–cellulose and piroxicam–chitosan mixtures.

Melting points and the enthalpies of piroxicam melting in all mixtures are summarized in Table 2. For comparison, the data for pure piroxicam, untreated and activated, are listed as well. It is interesting that the melting point of pure untreated piroxicam in our experiments (200.4°C) differs from that reported in the previous part of this work (200.7°C) [7]. We have analyzed the experimental conditions of all our measurements and came to the conclusion that the melting point of pure untreated piroxicam is subject to the heating rate. Probably, this phenomenon is related to the transformation of the piroxicam molecule into the zwitterion form during the melting [22]. Anyway, in our experiments the melting point of pure untreated piroxicam ranges within the limits of ±0.2°C. Mechanical treatment in the ball mill decreases the onset point by 0.6°C, indicating evidently that the activation does change the properties of piroxicam.

The mixing of piroxicam with the excipients, both cellulose and chitosan, decreases the melting point and the enthalpy of melting. The only reason we guess for the explanation of this fact is that the components of the mixture start to interact with each other at heating. Considering the effects of the activation and mixing as separate and independent, one could expect that the mechanical activation of an excipient will decrease the melting parameters of activated piroxicam in the mixture to the greater extent than those of untreated component in a mixture, for the reactivity of activated excipient is evidently greater than that of untreated one. Surprisingly, this is not the case. We especially repeated several experiments (‘Experimental’) to check these results, but found out that all the mixtures with components, untreated or activated separately, have similar melting parameters within the limits of experimental errors combined with the reproducibility of melting parameters of piroxicam. Activation of the mixture piroxicam–excipient produces very large effect: the melting decreases by 5–6°C, and the enthalpy of melting decreases as much as two times. This result shows evidently that piroxicam interacts with cellulose and chitosan, and the activation in a ball mill at room temperature improves the conditions for the drug-excipient interaction.

Piroxicam affecting the thermal destruction of excipients

Usually, the drug–excipient interaction is considered as a mechanism of the degradation of a drug substance in a drug formulation. Here, we faced the evidence of the thermal destruction of excipients, both cellulose and chitosan, stimulated by the drug, i.e., by piroxicam. Four DSC curves of piroxicam–chitosan mixtures are shown in Fig. 6. These are raw experimental data after the measurements, without any corrections or movements of the curves upward or downward. As we used crucibles and samples very close in their masses, the DSC signals turned out to be reproduced with very high precision. Before the melting of piroxicam, four curves in Fig. 6 fall into two groups: two with untreated chitosan (1 and 2) and two with activated (3 and 4). The lines of activated chitosan are slightly lower than those of untreated chitosan, and deflect more and more downward with increasing temperature. This is the increasing exothermic effect of the thermal destruction of chitosan that was described in Results (Fig. 1). The melting peaks of piroxicam de-

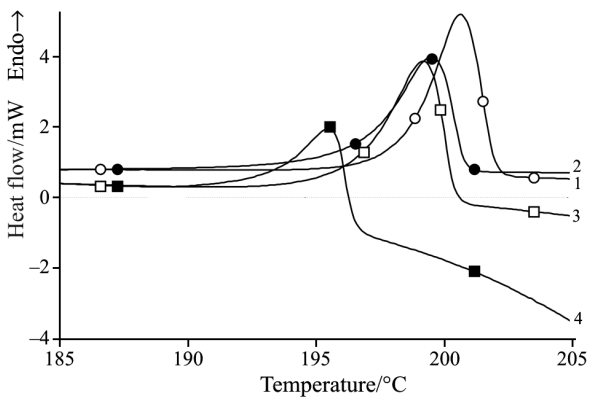


**Fig. 6** Raw DSC results of piroxicam–chitosan mixtures. The numerals indicate the mixtures like those in Fig. 5

pend on mechanical activation of the mixture. This was also discussed above. Here, we should focus on the differences between lines 3 and 4. The lines coincide with one another from the very start (170°C) to 190°C. Above that temperature piroxicam starts to melt in the mixture of components activated together (line 4). The melting finishes near 196°C, and then line 4 goes rapidly downwards, indicating exothermic thermal destruction of chitosan. It is the effect of chitosan, not of piroxicam, because piroxicam after its melting has additional endothermic contribution, not exothermic. It was shown in the previous report (Fig. 6 in [7]). For the mixture of components activated separately (line 3), the interaction between piroxicam and chitosan is less. It is evident from the smaller changes in the melting parameters of piroxicam in the mixture as compared to the pure untreated sample. Thus, we have the direct relation between the changes in the melting parameters of piroxicam and the exothermic contribution from the thermal destruction of chitosan.

*Comparison between cellulose and chitosan*

Application of cellulose and chitosan in the drug formulations of piroxicam will result in different biological availability of the latter. The solubility of piroxicam increases in the mixture with chitosan but remains unchanged with cellulose [9]. We measured the kinetics of piroxicam dissolution in water for the drug, pure or in the mixture with an excipient. The samples were used 'as such' or activated in the ball mills. The results for piroxicam–cellulose mixtures are shown in Fig. 7. Untreated piroxicam, both pure and in a physical mixture with cellulose (filled circles and squares), dissolves quite commonly. Its concentration in the solution arises steadily, tending to a constant value of conventional solubility. Activated piroxicam, pure or in mixture with cellulose, dissolves quite different. At the very start of the process the concentrations increases extremely rapidly, exceeding the equilibrium value of the solubility for a while. Then the concentration decreases down to the equilibrium value. Such an effect of temporary oversaturation at the very beginning of the drug dissolution in water from mechanically activated mixtures with microcrystalline cellulose was observed in [23]. It is interesting that the mixture of components activated together does not show the oversaturation. Nevertheless, the rate of dissolution also is much greater than that from untreated piroxicam. Probably, activated cellulose fibers absorb the 'activated' piroxicam molecules ready to dissolve in water, preventing the solution from the oversaturation. The results for the piroxicam–chitosan mixtures are similar, except one fundamental point: the equilibrium concentration of piroxicam in the water–chitosan–piroxicam solution increases significantly compared to the water–piroxicam one. The increase is about 0.4 g $L^{-1}$ for the mechanically activated mixture of 1:3 by mass and 0.65 g $L^{-1}$ for the same mixture of 1:10 [8]. In performing this work, we tried to clarify the reason of the difference in the interaction of piroxicam with these two excipients. The results are quite unexpected. Both excipients interact with piroxicam in the same way, resulting in the changes of melting parameters of piroxicam. Melting point and the enthalpy of piroxicam melting in all the samples (the physical mixture of untreated components, in the mixture of components activated separately and together) change similarly for both excipients. The results for cellulose and chitosan differ only quantitatively, not qualitatively, and the quantitative difference is close to the experimental reproducibility. So why has the difference in the solubility of piroxicam in the mixture with these excipients arisen?

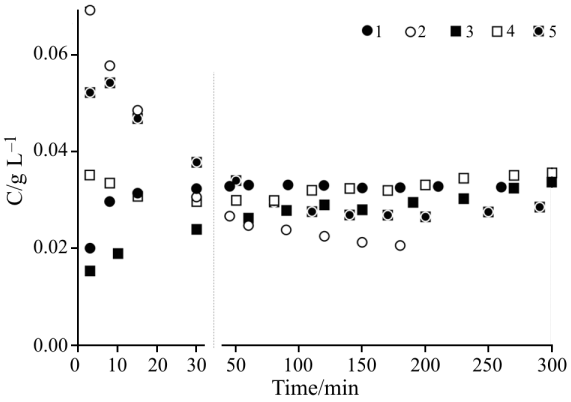


**Fig. 7** Kinetics of piroxicam dissolution in water: 1 – untreated piroxicam, 2 – activated piroxicam, 3 – mixture piroxicam+cellulose (1:3), 4 – the mixture activated, 5 – the mixture of the components activated separately

We think that the reason is the difference in the solubility of pure excipients. Pure chitosan is slightly water-soluble. This, among others, allows one to measure its viscosity-average molecular mass. Contrary, cellulose is insoluble in water. When piroxicam interacts with either excipient, its molecules contact with fibers, forming amorphous solids. X-ray powder diffraction patterns of activated mixture piroxicam-excipient show very weak reflections of crystalline piroxicam. When immersed into water, fibers of cellulose and chitosan behave differently. Cellulose fibers sorb water but the sample remains solid in bulk. Piroxicam molecules solely dissolve, but the solubility of pure piroxicam is low. Chitosan fibers interact with water, passing into the solution together with the piroxicam molecules fasten, forming the water-soluble unit with piroxicam molecule [8]. Thus, piroxicam disperses in water solvents, and its biological availability increases.

## Conclusions

DSC measurements of piroxicam melting in the mixtures with cellulose and chitosan reveal that the drug interacts with both excipients very similarly. Mechanical activation of the mixture components, together or separately, enlarges (activates) the interaction, making the changes in the melting parameters of piroxicam very large and easy to detect.

Besides the changes in the piroxicam properties, we found out that the drug–excipient interaction leads to the changes in the thermal stability of excipients, both cellulose and chitosan, decreasing the temperature of their thermal destruction and increasing the exothermic contribution to the DSC signal of the mixtures. Such a result establishes new task for the investigations of drug–excipient interactions, new facet of the general problem of drug–excipient compatibility.

The piroxicam–excipient interaction was found to be very similar for cellulose and chitosan, but the solubility of piroxicam and its biological availability increases only in the mixture with chitosan, not with cellulose. One of the reasons may be the difference in the solubility of excipients themselves: chitosan passes into water solution together with piroxicam molecules interacted with and fasten to chitosan fibers, whereas cellulose fibers remain in solid phase, again together with piroxicam molecules. This result shows that the detection of the interaction between drug and excipient solely is not enough to conclude about the compatibility of components in a drug formulation.

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## References

1 T. Durig and A. R. Fassihi, Int. J. Pharm., 97 (1993) 161.
2 N. Munoz, C. Ferrero, A. Munoz-Ruiz, M. V. Velasco and M. R. Jimenez-Castellanos, Drug Dev. Ind. Pharm., 24 (1998) 785.
3 P. Mura, A. Manderioli, G. Bramanti, S. Furlanetto and S. Pinzauti, Int. J. Pharm., 119 (1995) 71.
4 M. A. Holgado, M. Fernandez-Arevalo, J. M. Gines, I. Caraballo and A. M. Rabasco, Pharmazie, 50 (1995) 195.
5 C. E. P. Malan, M. M. De Villiers and A. P. Lotter, Drug Dev. Ind. Pharm., 23 (1997) 533.
6 G. Bruni, L. Amici, V. Berbenni, A. Marini and A. Orlandi, J. Therm. Anal. Cal., 68 (2002) 561.
7 V. A. Drebushchak, T. P. Shakhtshneider, S. A. Apenina, T. N. Drebushchak, A. S. Medvedeva, L. P. Safronova and V. V. Boldyrev, J. Therm. Anal. Cal., OnlineFirst, DOI: 10.1007/s10973-005-7024-x.
8 G. L. Ivashchenko, T. P. Shakhtshneider, V. V. Boldyrev, N. G. Bazarnova, A. S. Medvedeva and L. P. Safronova, Mendeleev Commun., 13 (2003) 3.
9 S. A. Apenina, T. P. Shakhtshneider, A. S. Medvedeva, L. P. Safronova and V. V. Boldyrev, Composites of piroxicam with chitosan and cellulose obtained by mechanical activation. Abstr. Int. Conf. ‘Mechanochemical Synthesis and Sintering’, Novosibirsk, Russia, June 14–18, 2004, p. 209.
10 T. P. Shakhtshneider and V. V. Boldyrev, Mechanochemical synthesis and mechanical activation of drugs. In: Reactivity of Molecular Solids, Ed. E. Boldyreva and V. Boldyrev, John Wiley and Sons Ltd., England 1999, p. 271.
11 V. A. Drebushchak, J. Therm. Anal. Cal., 79 (2005) 213.
12 K. C. Jindal, R. S. Chaudhary, S. S. Gangwal, A. K. Singla and S. Khanna, J. Chromatogr. A, 685 (1994) 195.
13 G. M. Eccleston, Colloids Surf. A, 123 (1997) 169.
14 E. A. Schmitt, K. Peck, Y. Sun and J. M. Geoffroy, Thermochim. Acta, 380 (2001) 175.
15 V. J. Ndlebe, M. E. Brown and B. D. Glass, J. Therm. Anal. Cal., 77 (2004) 445.
16 S. C. Pinzaru, I. Pavel, N. Leopold and W. Kiefer, J. Raman Spectrosc., 35 (2004) 338.
17 R. O. Macedo, T. G. do Nascimento and J. W. E. Veras, J. Therm. Anal. Cal., 67 (2002) 483.
18 F. S. de Souza, R. O. Macedo and J. W. E. Veras, Thermochim. Acta, 392 (2002) 99.
19 A. Marini, V. Berbenni, M. Pegoretti, G. Bruni, P. Cofrancesco, C. Sinistri and M. Villa, J. Therm. Anal. Cal., 73 (2003) 547.
20 A. Marini, V. Berbenni, S. Moioli, G. Bruni, P. Cofrancesco, C. Margheritis and M. Villa, J. Therm. Anal. Cal., 73 (2003) 529.
21 G. G. G. Oliveira, H. G. Ferraz and J. S. R. Matos, J. Therm. Anal. Cal., 79 (2005) 267.
22 A. R. Sheth, J. W. Lubach, E. J. Munson, F. X. Muller and D. J. W. Grant, J. Am. Chem. Soc., 127 (2005) 6641.
23 Y. Nakai, E. Fukuoka, S. Nakajima and K. Yamamoto, Chem. Pharm. Bull., 25 (1977) 3340.

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