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THERMOANALYTICAL INVESTIGATION OF DRUG-EXCIPIENT INTERACTION
Part I. Piroxicam, cellulose and chitosan as starting materials

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Cellulose, chitosan and piroxicam were investigated by TG and DSC at heating up to 215°C, and by X-ray powder diffraction before and after the heating.

Dehydration of cellulose and chitosan comes to the end near 160°C. Thermal decomposition of chitosan starts at the final stage of its dehydration, and the mass losses after these two reactions overlap with one another. Enthalpy of dehydration is 47.1±2.4 kJ mol^{-1} of water for cellulose and 46.2±2.0 kJ mol^{-1} for chitosan. Thermal decomposition of chitosan is an exothermic process. Crystal structure of cellulose after heating remains unchanged, but that of chitosan contracts.

Piroxicam melts at 200.7°C with the enthalpy of melting 35 kJ mol^{-1}. Heat capacity of the liquid phase is greater than that of the solid phase by approximately 100 J mol^{-1} K^{-1}. Cooled back to ambient temperature, piroxicam remains glassy for a long time, crystallizing slowly back into the starting polymorph.

Keywords: *cellulose, chitosan, dehydration, DSC, melting, piroxicam, TG, thermal decomposition*

Introduction

Drug formulation is a very important characteristic of contemporary drugs, rather than only the active substance. Crystal form of the active substance, its dispersity, fillers, etc., affect the rate of dissolution of the drug, its shelf time, combination of different active substances in one tablet, etc. Correct drug formulation is to ensure that the dissolved active substance reaches the target organ in the right concentration for a desired period of time.

Cellulose and chitosan are used widely as excipients in solid drug formulations, e.g., tablets, where the active substance is another solid [1, 2]. Often, the latter is represented with molecular crystals. Piroxicam belongs to the oxicam group of non-steroidal anti-inflammatory drugs. It is used for the treatment of inflammation and pain that results from rheumatoid arthritis and osteoarthritis.

Crystallinity, grinding, nitrogen gas and water vapor adsorption, heat of wetting, and compression of microcrystalline cellulose was investigated in [3], its structure, surface features and water sorption capability in [4]. Interaction of water with the regenerated cellulose membrane was studied by DSC [5]. Thermal degradation of cellulose was described in [6, 7]. Applications of chitosan as a pharmaceutical drug carrier were reviewed in [8]. There are published data on thermal characteristics of chitosan [9, 10], water vapor sorption [11], and thermodynamics of water–chitosan mixing [12]. Thermal degradation of chitosan in nitrogen and air was described in [13]. Structure of piroxicam was investigated in [14–16]. Its synthesis, optical (IR and UV) properties, NMR, solution properties, thermal and photostability, and pharmaceutical properties are reviewed in [17]. DSC measurements showed that the samples crystallized from various solvents range in the melting point (200.6 to 201.8°C) and enthalpy of melting (29.1 to 133.2 J g^{-1}) [18].

The objective of this work was to investigate thermal properties of the pure components of solid drug formulations (cellulose and chitosan) and of an active substance (piroxicam) separately and in mixture, untreated and mechanically activated. In the first part we report the results of the investigations of untreated pure starting materials.

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Experimental

Samples

Microcrystalline cellulose was a commercial chemical product. The sample is a snow-white fine powder. After heating to 220°C in dry argon its color has changed to very light brown shade.

Chitosan was produced from the chitin of Far Eastern crabs according to technical specifications TY-9289-058-04689375 and purchased from OAO Reaktiw (Russia). The viscosity-average molecular mass is $4 \cdot 10^7$. The sample consists of yellow flocks. After heating to 220°C in dry argon the yellow color becomes more intense, with light red shade.

Water content of cellulose and chitosan depends on humidity. No special experiments on the investigation of the relationship between the water content and humidity for our samples were carried out. In the DSC and TG experiments we used air-dry samples, measuring the water content of the sample each time.

Piroxicam ($C_{15}H_{13}N_3O_4S$–CAS# 36322-90-4, 4-hydroxy-2-methyl-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide, formula mass 331.35) was synthesized at A. E. Favorsky Irkutsk Institute of Chemistry, SB RAS, according to original procedure of patents [19, 20]. There are two polymorphs of piroxicam, differing in the way by which the hydrogen atoms contact with other atoms in the molecule and, hence, in the arrangement of molecules in the crystal structure [14, 16]. There is a discrepancy in the designation of physical and chemical properties (structure, DSC data, IR spectra, etc.) to a particular polymorph (α, β, γ, etc.) [14, 15]. To avoid the discussion, we report that our sample was a white powder with the unit cell parameters as follows: a=7.1357(2), b=15.1595(8), c=13.9640(7) Å, β=97.383(4)°. The lattice parameter refinement was proceeded with TOPAS software for the whole powder pattern fitting. The X-ray powder diffraction pattern was measured using D8-GADDS (Bruker) diffractometer. The experimental XRPD pattern of piroxicam is shown in Fig. 1. The reflections derived from the refinement are listed in Table 1. Only 9 first peaks in the pattern (Fig. 1) are individual reflections, well separated from others. The rest reflections start to overlap with one another. All peaks with 2θ>17° are formed by the superposition of two or more close reflections.

Equipment

Thermogravimetric measurements were carried out using TG-209 (Netzsch) with an aluminum crucible in an atmosphere of dry argon (25 mL min^{-1}). The experiments were performed over the temperature range 25 to 220°C at a heating rate of 6°C min^{-1}. Sample mass was 20.170 mg for cellulose, 20.175 mg for chitosan, and 20.185 mg for piroxicam. Measured values $m(T)$ were corrected for the blank experiment (empty crucible).

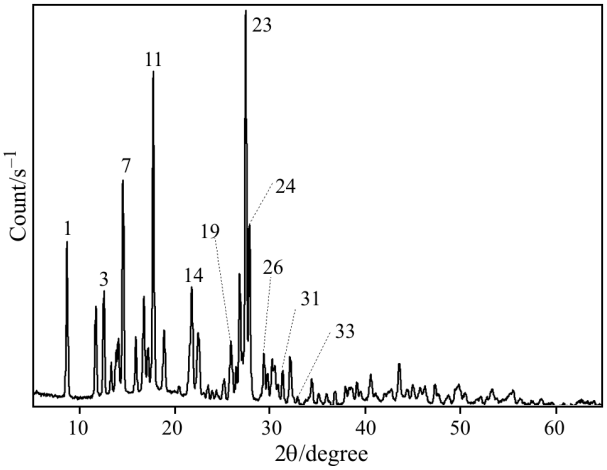

Fig. 1 X-ray powder diffraction of piroxicam (CuK$_\alpha$ radiation); the peaks are numerated left to right to compare them with the reflections in Table 1

Calorimetric measurements were carried out using DSC-204 (Netzsch) with a standard aluminum crucible of 40 mL covered with a lid, but not sealed, in an atmosphere of dry argon (25 mL min^{-1}). Freely lying lid does not prevent dehydration of a sample, for water vapor escapes due to the excess pressure inside crucible, but prevents the rehydration, for water molecules have to diffuse back under the lid from surroundings. Similarly, freely lying lid does not prevent sublimation of piroxicam. The calorimeter was calibrated against enthalpy of fusion of Ga, In, and Zn according to optimized calibration procedure [21, 22] and tested after heat capacity measurements of corundum at scanning heating. All the calorimetric experiments were performed at a heating rate of 6°C min^{-1}. Piroxicam was heated from 20 to 215°C. Cellulose and chitosan were measured twice for every sample to extract the heat effect of dehydration. First, cellulose and chitosan were heated from 20 to 215°C, but then we had to repeat the experiments starting from –30°C. For chitosan, the upper temperature limit was decreased to 195°C. It was found that at heating above 200°C chitosan changes significantly and irreversibly, changing its heat capacity in such a way that the difference between first and second heating is not the result of dehydration only. For cellulose and chitosan, sample mass was measured before the first and after the second run. The sample mass was derived from a series of 16 weighings one by one with an interval of 40 s. Mass of cellulose and chitosan after the measurements drifted, indicating their rehydration. The difference between starting and final (after the experiment) mass was considered to be the water content of the sample.

Table 1 The results of cell parameters refinement after the profile of the X-ray powder diffraction pattern of piroxicam; *N* is the number of a peak seen on Fig. 1

d	*I*	*h k l*	*N*	*d*	*I*	*h k l*	*N*
10.2244	66	0 1 1	1	3.2938	63	1 2 3	22
7.5797	71	0 2 0	2	3.2936	108	1 4 –1	22
7.0765	96	1 0 0	3	3.2807	2	1 0 –4	22
6.6489	31	0 2 1	4	3.2514	802	2 1 –2	23
6.4123	44	1 1 0	5	3.2498	1000	2 1 1	23
6.2982	59	0 1 2	6	3.2067	127	2 2 –1	24
6.0957	245	1 1 –1	7	3.2065	478	1 1 –4	24
5.5765	86	1 1 1	8	3.2062	9	2 2 0	24
5.3013	165	1 0 –2	9	3.2037	255	1 4 1	24
5.1726	79	1 2 0	10	3.1912	2	1 3 –3	24
5.1122	11	0 2 2	10	3.0831	32	1 4 –2	25
5.0042	520	1 1 –2	11	3.0479	72	2 2 –2	26
5.0021	121	1 2 –1	11	3.0466	218	2 2 1	26
4.7470	20	0 3 1	12	3.0108	142	1 2 –4	27
4.7030	138	1 2 1	12	2.9985	47	2 0 2	27
4.6589	7	1 0 2	12	2.9632	1	1 0 4	28
4.3442	13	1 2 –2	13	2.9627	2	1 3 3	28
4.1123	162	1 3 0	14	2.9618	242	0 5 1	28
4.0818	276	0 3 2	14	2.9434	91	2 1 –3	29
4.0251	13	1 3 –1	15	2.9415	8	2 1 2	29
3.9720	100	1 1 –3	15	2.9400	23	1 4 2	29
3.9691	70	1 2 2	15	2.9291	178	0 4 3	29
3.9425	116	0 2 3	15	2.9081	25	1 1 4	30
3.7899	29	0 4 0	16	2.8988	19	2 3 –1	30
3.6577	5	1 3 –2	17	2.8984	80	2 3 0	30
3.6555	10	0 4 1	17	2.8560	222	0 3 4	31
3.5552	22	1 1 3	18	2.7899	174	2 2 –3	32
3.5383	64	2 0 0	18	2.7882	51	2 2 2	32
3.4621	6	0 0 4	19	2.7880	53	1 4 –3	32
3.4463	120	2 1 –1	19	2.7869	44	1 5 0	32
3.4457	85	2 1 0	19	2.7799	19	2 3 –2	32
3.4253	116	1 3 2	19	2.7789	20	2 3 1	32
3.3752	136	0 1 4	20	2.7773	35	0 5 2	32
3.3409	7	1 4 0	21	2.7598	32	1 2 4	33
3.3288	339	2 0 –2	21	2.7593	5	1 5 –1	33
3.3245	233	0 4 2	21				

X-ray powder diffraction patterns of the samples were measured using D8-GADDS (Bruker) diffractometer with CuK_α radiation in rotating sample holder. Complete patterns of starting materials were derived from the measurements over three intervals (frames) of angles 2θ: 5–25, 25–45 and 45–65°, those of cellulose and chitosan after thermogravimetric experiments were derived from two frames, 5–25 and 25–45°C.

Results

Thermogravimetry

Mass losses at heating for cellulose, chitosan and piroxicam are shown in Fig. 2a. Dehydration of cellulose starts at room temperature and finishes at about 150°C. The TG experiments shown in Fig. 2a were carried out in summer (early August, mean temperature about 20°C) under high humidity conditions.

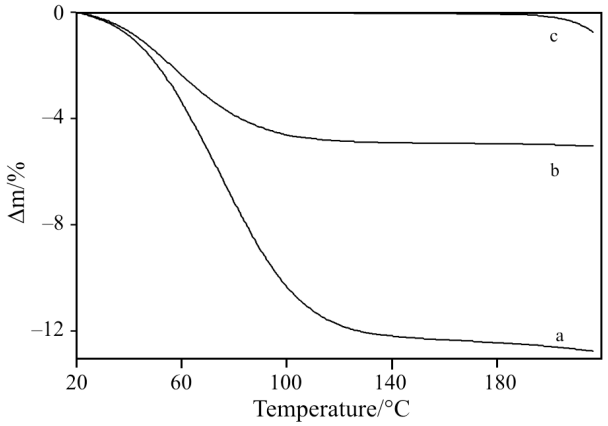

Fig. 2a Mass loss at heating for a – chitosan, b – cellulose and c – piroxicam

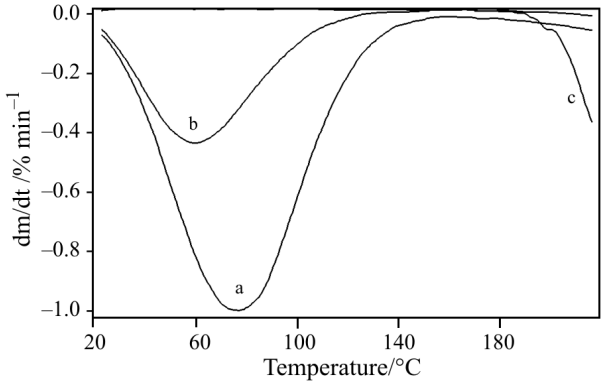

Fig. 2b The rate of mass loss for a – chitosan, b – cellulose and c – piroxicam

Water content of cellulose turned out to be 4.9%. At heating above 200°C, the decrease in mass starts again and the additional value of mass loss at heating to 215°C is of 0.1%. This is the thermal decomposition of cellulose. It can be seen better in Fig. 2b, where the experimental results are shown as the derivatives of the mass loss with respect to time. Partly decomposed sample changes its color from white-snow to a light-cream shade.

X-ray powder diffraction patterns of cellulose before and after the TG experiments are shown in Fig. 3. The positions of the peaks remain unchanged. Small changes in the intensity of the peaks and background for angles below 24° are there only.

Chitosan loses its mass like cellulose. It starts to dehydrate at the very beginning of the heating, forming a peak at ~70°C. Then the rate of the mass loss decreases, but not to zero. Minimal value of 0.03% min^{-1} is at 160°C. Then the rate of mass loss increases again, now due to the thermal decomposition. Overall, chitosan loses 12.3% at heating to 160°C and another 0.4% to 215°C. After the experiment the sample has changed its light-yellow color to heavy yellow.

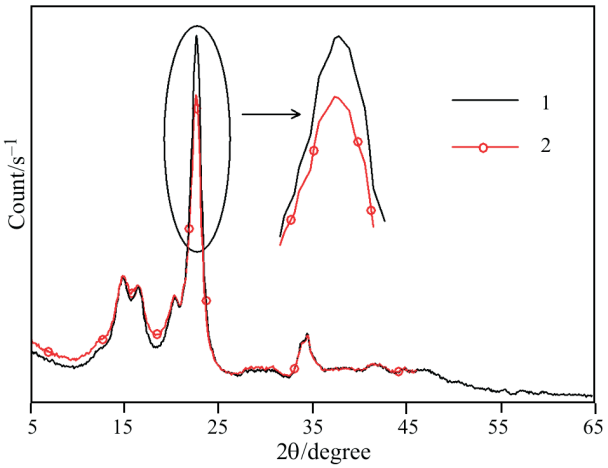

Fig. 3 X-ray powder diffraction of cellulose 1 – before and 2 – after the heating to 215°C

X-ray powder diffraction patterns of chitosan before and after the TG experiments are shown in Fig. 4. The peaks of heated sample move evidently toward greater angles 2θ, indicating the decrease in the interplanar distances of crystalline structure of chitosan. This is mainly the result of dehydration, not thermal decomposition, for we stopped the heating at the very beginning of the second stage of the mass loss. Nevertheless, unlike cellulose, the dehydration of chitosan changes gradually into thermal decomposition, and it is difficult to define the exact temperature limit where this change takes place.

Mass of piroxicam remains nearly constant at heating up to 150°C. Then the rate of mass loss increases exponentially: 0.1% min^{-1} at 188°C, 0.2 at 203°C, 0.4 at 211°C, and 0.8% min^{-1} at 220°C (Fig. 2b). The sample vaporizes and simultaneously it melts near 200°C. Cooled down to room temperature, the sample does not crystallize immediately but re-

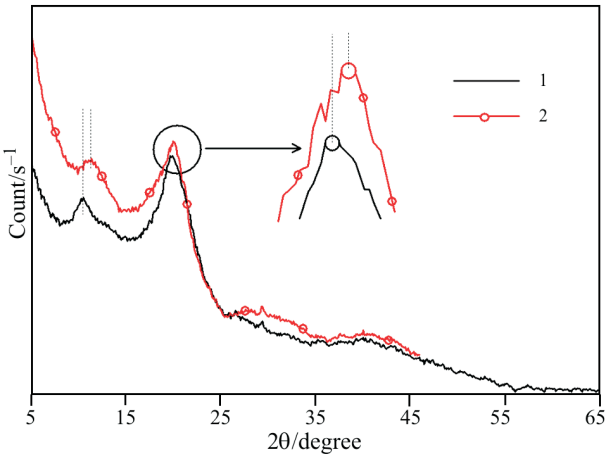

Fig. 4 X-ray powder diffraction of chitosan 1 – before and 2 – after the heating to 215°C; the inserts show the shift in the position of peaks at 11 and 18°

mains glassy for a long time, looking like a brown drop. Stored in the crucible for 1–2 months after the experiment, the sample is covered here and there with a dim skin, then transforming into nodules turning white, remaining brown in massive. An X-ray powder diffraction pattern of such an aged sample is identical with that of starting material. In the experiments on mechanical activation of piroxicam, the reversible change in color was suggested to be the result of partial transformation of piroxicam molecules into zwitter-ion form [23], later proved experimentally [24].

Differential scanning calorimetry

The results of calorimetric measurements of cellulose and chitosan in a temperature range of 20 to 215°C are shown in Fig. 5. Starting sample mass was 17.945 mg for cellulose and 17.210 mg for chitosan. Each sample was measured in two runs, one by one. The difference in the results between these two runs for each sample is the pure heat effect of dehydration. As water content of chitosan is greater than that of cellulose, the total heat effect of the dehydration for chitosan is greater than that for cellulose. Dehydration of cellulose comes to the end near 160°C and after that the DSC signal (heat capacity) grows steady with temperature. Dehydration of chitosan seems to continue nearly to 200°C, but this is not quite right. One should remember that the mass loss of chitosan above 160°C is partly caused by the thermal decomposition. Near 200°C, the lines of two runs coincide with one another and deflect together downward, indicating that the heat effect of thermal decomposition of chitosan is exothermic.

The calorimetric experiments were performed in October, when the average outdoor temperature was about –5°C. The indoor humidity was much lower than that in August during the TG experiments, and water content of cellulose and chitosan turned out to be 3.1 and 8.3%, respectively. These values are less than those in TG experiments are (4.9 and 12.3%, respectively). Similar mass-variability was observed in the experiments with chitosan: 4.8 and 3.4% at the heating 'under N_2 and air atmosphere' [13]. It is interesting, that the samples were reported to be dried in a vacuum oven at 60°C for 20 h, and no information about subsequent rehydration was mentioned. Probably the samples sorbed water when they were stored under ambient conditions.

In the DSC curves of our samples we did not find the irregularities, similar to those published in [25]. Peak of dehydration for our samples is broad and smooth, typical of sorbents without phase transitions.

To measure the enthalpy of dehydration, we repeated the calorimetric measurements of cellulose and chitosan in two runs, but started the runs from –30°C in order to measure correctly, without distortion by dehydration, the starting baseline in the experiments. Upper temperature limits of new measurements were 215°C for cellulose and 195°C for chitosan. This was decreased in order to diminish the changes in the chitosan at the decomposition. Evaluations of the enthalpy of dehydration are described in the next paragraph.

DSC results for piroxicam are shown in Fig. 6. The signal is smooth and increases steady up to the melting point (200.7°C). Enthalpy of melting is 35.0 kJ mol^{-1} K^{-1} (105.6 kJ g^{-1} K^{-1}). The changes in the heat flow in the vicinity of the melting point are shown in detail on the insert of Fig. 6. DSC signal after the melting is greater than that before by 0.03 W g^{-1} what is equivalent to the difference in the heat capacity by 0.3 J g^{-1} K^{-1} or ~100 J mol^{-1} K^{-1}.

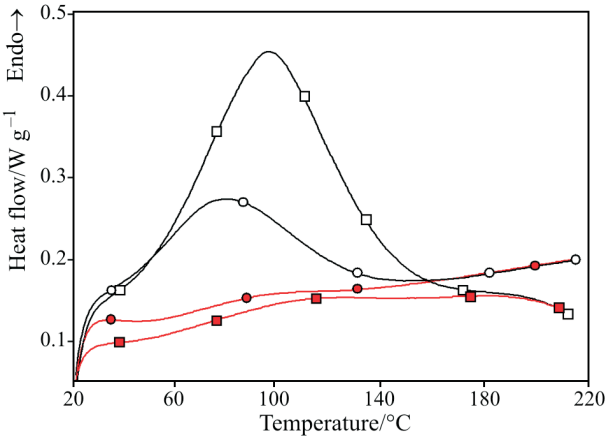

Fig. 5 DSC measurements of cellulose (circles) and chitosan (squares). The first heating is marked with open marks, the second one with filled those

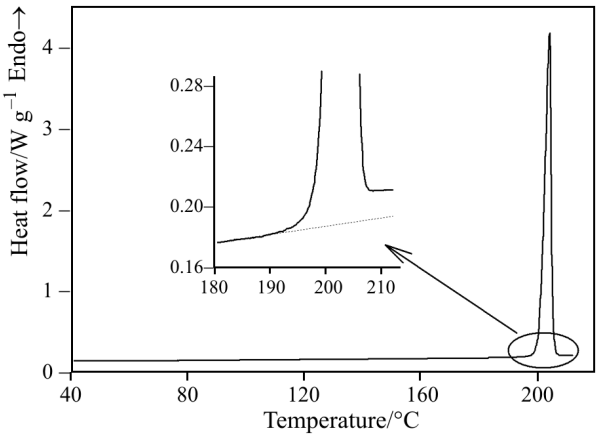

Fig. 6 DSC measurements of piroxicam; the increase in the DSC signal after the melting is seen well on the insert

Discussion

Dehydration of cellulose and chitosan

Cellulose differs from chitosan in the water content and thermal stability. It is interesting to recognize whether these two samples differ in the energy of water-excipient interaction.

Figure 7 shows the difference between the first and second runs for both substances recalculated to the 'heat capacity' of water in the sample according to equation

$$\frac{dQ}{dT} = \frac{1}{m_0}\frac{W_1 - W_2}{\beta} \quad (1)$$

where m_0 is the starting mass of water in the sample, β is the heating rate, W_1 and W_2 are the DSC signals at the first and second runs, respectively. At temperatures below 0°C there is no dehydration in cellulose and chitosan. The extra heat flow in the samples is the conventional heat capacity:

$$\frac{dQ}{dT} = C_P \quad (2)$$

Cellulose and chitosan start to dehydrate at heating above room temperature, and additional contribution to the heat flow appears. This is proportional to the product of the rate of mass loss (dm/dT) and normalized enthalpy of dehydration (q). The contribution from the conventional heat capacity decreases together with the mass of water $m(T)$ remaining in the sample:

$$\frac{dQ}{dT} = \frac{1}{m_0}\left[m(T)C_P + \frac{dm}{dT}q\right] \quad (3)$$

Current water content of a sample and the rate of mass loss are connected by relationship

$$m(T) = m_0 - \int_{T_0}^{T}\frac{dm}{dT}dT \quad (4)$$

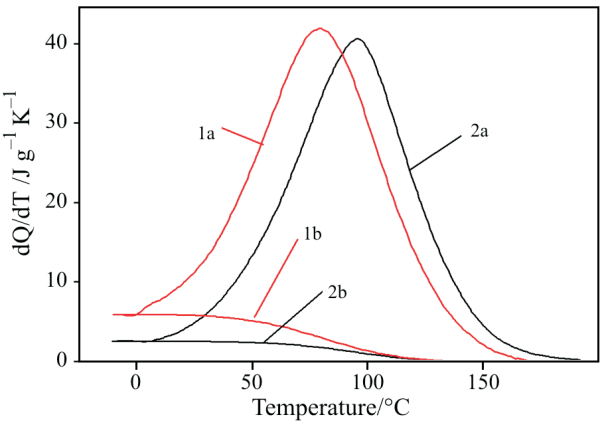

Fig. 7 The contribution from the dehydration as a difference between the first and second heating for 1a – cellulose and 2a – chitosan. Heat capacity of water decreases with temperature: 1b – cellulose, 2b – chitosan

Combination of TG results (m and dm/dT) with those of DSC (dQ/dT) allows one to evaluate the partial molar heat of dehydration $q(x)$ for any interval of water content in a sample (x=m/m_0). The procedure was described in detail for the dehydration of zeolites, where the water molecules occupy different sites in the crystal structure and phase transitions at dehydration take place [26]. As for cellulose and chitosan, it is sufficient to evaluate the average enthalpy of dehydration, for no steps in the dehydration are seen at TG and DSC curves. In considering the heat capacity of water molecules and enthalpy of dehydration constant (C_P=const, q=const), one can solve the set of two differential Eqs (3) and (4) by the iteration method, and extract the contribution of the heat capacity of water molecules. The results of the evaluations of function $[m(T)/m_0]C_P$ are shown in Fig. 7 by lines 1b and 2b for cellulose and chitosan, respectively. The average enthalpy of dehydration is the area between lines (a) and (b):

$$q = \int_{T_0}^{T_1}\frac{dQ}{dT}dT - C_P\frac{1}{m_0}\int_{T_0}^{T_1}m(T)dT \quad (5)$$

The values of q are 47.1±2.4 kJ mol^{-1} (H_2O) for cellulose and 46.2±2.0 kJ mol^{-1} (H_2O) for chitosan. Uncertainty in the value of q is a sum of three contributions: uncertainty in 1) the DSC signal after replacing crucible inside the calorimeter (~3%), 2) calibration of the DSC sensor (~1%), and 3) m_0 value (1% for cellulose and 0.3% for chitosan). The values of q for cellulose and chitosan are equal within the limits of experimental errors. Besides, the small excess in q can be the result of the difference in average temperature of dehydration for cellulose and chitosan caused by the greater water content of chitosan. The maximum of the dehydration peak is at 80°C for cellulose but 95°C for chitosan. Enthalpy of evaporation of pure water is 45.0 kJ mol^{-1} at 0°C, 42.8 at 50°C, 40.7 at 100°C and 38.1 kJ mol^{-1} at 150°C [27].

Water contribution to the heat capacity (C_p) turned out to be 110±6 and 49±2 J mol^{-1} K^{-1} for cellulose and chitosan. The difference between these values exceeds the limits of experimental errors. We repeated the low-temperature measurements to ensure that such significant difference is not the result of a single erroneous experiment. The result has reproduced. Heat capacity of pure water at room temperature is about 75 J mol^{-1} K^{-1} and this value is considered very high. Typical values for the water contribution to the heat capacity of sorbents range from 35 to 70 J mol^{-1} K^{-1}.

Heat of wetting of microcrystalline cellulose was measured in [3], but the results cannot be compared with ours. We measured the heat of dehydration with the control of water content, but in [3] the heat was measured in the experiment without such a control.

Conclusions

Heating of pure cellulose and chitosan results at first in their dehydration and then in thermal destruction. Cellulose and chitosan lose water very similarly, except the total mass loss and minor changes in structure: chitosan slightly contracts at dehydration but cellulose remains unchanged. This may cause the destruction of the chitosan-rich tablets after several wetting-drying cycles during long-term storage of drugs under ambient conditions. On the other hand, by the same reason a tablet with chitosan disintegrates in the body more readily than that with cellulose.

Thermal decomposition of chitosan starts at temperatures lower than that of cellulose: at heating above 200°C the structure of chitosan changes, accompanied by an exothermic effect, but the crystal structure of cellulose remains unchanged after heating to 215°C, and no thermal anomalies are there on DSC curve.

Piroxicam has no anomalies in the heat capacity at heating from room temperature to its melting point (200.7°C). Enthalpy of melting is 35 kJ mol^{-1}. Heat capacity of liquid piroxicam is greater than that of solid phase by 100 J mol^{-1} K^{-1}.

The results of this work are to be used as the reference data in the investigation of piroxicam-(cellulose, chitosan) interaction in untreated and mechanically activated mixtures.

Acknowledgements

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