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(54) Titre : UNE FORME POLYMERIQUE DE 1-((4-METHYL-QUINAZOLIN-2-YL)METHYL)-3-7-(2-BUTYN-1-YL)-8-(3-(R)-AMINOPIPERIDIN-1-YL)XANTHINE

(54) Title: A POLYMERIC FORM OF 1-((4-METHYL-QUINAZOLIN-2-YL)METHYL)-3-7-(2-BUTYN-1-YL)-8-(3-(R)-AMINOPIPERIDIN-1-YL)XANTHINE

(57) Abrégé/Abstract:
The invention relates to polymorphic crystal modifications of 1-((4-methyl-quinazolin-2-yl)methyl)-3,7-(2-butyn-1-yl)-8-(3-(R)-aminopiperidin-1-yl)xanthine, their production and their use for the preparation of a medicament.

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ABSTRACT

The invention relates to polymorphic crystal modifications of 1-((4-methyl-quinazolin-2-yl)methyl)-3,7-(2-butyn-1-yl)-8-(3-(R)-aminopiperidin-1-yl)xanthine, their production and their use for the preparation of a medicament.

A Polymeric Form of 1-((4-methyl-quinazolin-2-yl)methyl)-3-7-(2-butyn-1-yl)-8-(3-(R)-aminopiperidin-1-yl)xanthine

This application is a division of Canadian Application Serial No. 2,651,089 (parent application), filed April 30, 2007.

It should be understood that the expression "the present invention" or the like used in this specification may encompass not only the subject matter of this divisional application, but that of the parent application also.

The invention relates to polymorphous crystal modifications of a DPP-IV inhibitor, the preparation thereof and the use thereof for preparing a medicament.

The enzyme DPP-IV, also known by the name CD26, is a serine protease which promotes the cleaving of dipeptides in proteins with a proline or alanine group at the N-terminal end. DPP-IV inhibitors thereby influence the plasma level of bioactive peptides including the peptide GLP-1. Compounds of this type are useful for the prevention or treatment of illnesses or conditions which are associated with an increased DPP-IV activity or which can be prevented or alleviated by reducing the DPP-IV activity, particularly type I or type II diabetes mellitus, prediabetes, or reduced glucose tolerance.

WO 2004/018468 (CA 2,496,249) describes DPP-IV inhibitors with valuable pharmacological properties. One example of the inhibitors disclosed therein is 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine. WO 2004/018468 discloses an IC_{50}[nM]=1 for this compound in a DPP-IV assay that was carried out as follows:

An extract of human colon carcinoma cell line Caco-2 was used as the DPP-IV source. The differentiation of the cells in order to induce the DPP-IV expression was carried out as described by Reiher et al. in an article entitled "Increased expression of intestinal cell line Caco-2", which appeared in Proc. Natl. Acad. Sci. Vol. 90, pages 5757-5761 (1993). The cell extract was obtained from cells solubilised in a buffer

(10mM Tris HCl, 0.15 M NaCl, 0.04 t.i.u. aprotinin, 0.5% Nonidet™-P40, pH 8.0) by centrifuging at 35,000 g of for 30 minutes at 4°C (to remove cell debris).

50 µl substrate solution (AFC; AFC is amido-4-trifluoromethylcoumarin), final concentration 100 µM, were placed in black microtitre plates. 20 µl of assay buffer (final concentrations 50 mM Tris HCl pH 7.8, 50 mM NaCl, 1% DMSO) was pipetted in. The reaction was started by adding 30 µl of solubilised Caco-2 protein (final concentration 0.14 µg of protein per well). The test substances to be investigated were typically added prediluted in 20 µl, and the volume of assay buffer was then reduced accordingly. The reaction was carried out at ambient temperature, incubating for 60 minutes. Then the fluorescence was measured in a Victor™1420 Multilabel Counter, the excitation wavelength being 405 nm and the emission wavelength being 535 nm. Blank readings (corresponding to 0% activity) were obtained in mixtures without any Caco-2 protein (volume replaced by assay buffer), control values (corresponding to 100% activity) were obtained in mixtures with no substance added. The potency of the test substances in question, expressed as IC_{50} values, was calculated from dosage/activity curves consisting of 11 measuring points in each case.

Within the scope of the present invention it has been found that 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine may take on various polymorphous crystal modifications and that the compound prepared in WO2004/018468 is present at ambient temperature as a mixture of two enantiotropic polymorphs. The temperature at which the two polymorphs transform into one another is 25±15°C (see Figures 1 and 2).

The pure high temperature form (polymorph A), which can be obtained by heating the mixture to temperatures >40°C, melts at 206±3°C. In the X-ray powder diagram (see Figure 3) this form shows characteristic reflexes at the following d values: 11.59 Å, 7.60 Å, 7.15 Å, 3.86 Å, 3.54 Å and 3.47 Å (cf. also Table 1 and 2).

Anhydrous polymorph A may be prepared by

(a) refluxing 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine in absolute ethanol and optionally filtering the mixture,
(b) cooling the hot solution or the hot filtrate until crystallisation sets in,
(c) diluting with a solvent such as tert.-butylmethylether,
(d) suction filtering the solvent mixture and
(e) drying the polymorph A at 45°C *in vacuo*.

The low temperature form (polymorph B) is obtained by cooling to temperatures <10°C. In the X-ray powder diagram (see Figure 4) this form shows characteristic reflexes at the following d values: 11.25 Å, 9.32 Å, 7.46 Å, 6.98 Å and 3.77 Å (cf. also Table 3 and 4).

Anhydrous polymorph B may be prepared by
(a) dissolving 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine in absolute ethanol and refluxing and optionally filtering the mixture,
(b) cooling the hot solution or the hot filtrate for crystallisation to a temperature below 10°C,
(c) diluting with a solvent such as tert.-butylmethylether,
(d) suction filtering the solvent mixture and
(e) drying the polymorph at a temperature below 10°C *in vacuo*,
or by cooling anhydrous polymorph A or a mixture of polymorphs A and B to temperatures <10°C.

Another polymorph (polymorph C) shows characteristic reflexes in the X-ray powder diagram (see Figure 5) at the following d values: 12.90 Å, 11.10 Å, 6.44 Å, 3.93 Å and 3.74 Å (cf. also Table 5).

Polymorph C is obtained if
(a) 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine is dissolved in methanol and refluxed and optionally filtered in the presence of activated charcoal,
(b) the methanolic solution is cooled to a temperature of 40-60°C,

(c) a solvent such as tert.-butylmethylether or diisopropylether is added,

(d) the resulting suspension is first of all cooled slowly to 15-25°C and then later to 0-5°C,

(e) the crystals formed are suction filtered and washed again with tert.-butylmethylether or diisopropylether and

(f) the crystals thus obtained are dried at a temperature of 70°C in the vacuum dryer.

Another polymorph (polymorph D) melts at 150±3 °C. This polymorph is obtained if polymorph C is heated to a temperature of 30-100°C or dried at this temperature.

Finally, there is also polymorph E, which melts at a temperature of 175±3°C. Anhydrous polymorph E is formed if polymorph D is melted. On further heating, polymorph E crystallises out of the melt.

The polymorphs thus obtained may be used in the same way as the mixture of the two polymorphs A and B described in WO 2004/018468 for preparing a pharmaceutical composition which is suitable for treating patients with type I and type II diabetes mellitus, prediabetes or reduced glucose tolerance, with rheumatoid arthritis, obesity, or calcitonin-induced osteoporosis, as well as patients in whom an allograft transplant has been carried out. These medicaments contain in addition to one or more inert carriers at least 0.1% to 0.5%, preferably at least 0.5% to 1.5% and particularly preferably at least 1% to 3% of one of the polymorphs A, B, or C.

The inventions disclosed in this application include a formulation comprising the polymorph A and the polymorph B.

The present invention is also directed to a medicament containing anhydrous polymorph B of the compound 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine, wherein said medicament contains 0.1% to 0.5%, or 0.5% to 1.5%, or 1% to 3% of anhydrous polymorph B in addition to one or more inert carriers, wherein anhydrous polymorph B is characterised in that at a temperature of 10-40°C it transforms reversibly into anhydrous polymorph A of the compound 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-y1)-xanthine which melts at 206±3°C.

The following Examples are intended to illustrate the invention in more detail.

Example 1 **Crystallisation of polymorph A**

Crude 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine is refluxed with 5 times as much absolute ethanol and the hot solution is filtered clear through activated charcoal. After the filtrate has been cooled to 20°C and crystallisation has set in, the solution is diluted to double the volume with tert.-butylmethylether. Then the suspension is cooled to 2°C, stirred for 2 hours, suction filtered and dried in the vacuum dryer at 45°C.

Polymorph A melts at 206 ± 3 °C. In the DSC diagram another slightly endothermic signal can be seen at approx. 25°C. This is a fully reversible solid-solid phase transition between the two enantiotropic crystal modifications A and B. The form A is the thermodynamically stable modification above this transformation temperature, while form B is the thermodynamically stable modification below this transformation temperature.

Figure 2 shows a cyclic DSC diagram, in which the phase transition from -40 °C to 120 °C and *vice versa* has been run through a total of 3 times. During heating, the phase transition is observed as an endothermic signal and, correspondingly, during cooling it is observed as an exothermic signal. During the first heating cycle the phase transition may also be observed as an endothermic double signal or as a very broad signal while in all the other cycles the signal occurs as a very sharp endothermic or exothermic signal, depending on whether heating or cooling is taking place.

Table 1: Labelled X-ray reflexes up to 30 ° 2 Θ with intensities (standardised) for the anhydrous polymorph A

2 Θ	intensity	d_{hkl}	labelling			$d_{exp-calc}$
[°]	I/I_o [%]	[Å]	h	k	l	[Å]
5.56	1	15.89	1	0	0	-0.008
7.18	32	12.31	0	1	1	0.005
7.62	100	11.59	1	1	0	0.007
8.49	20	10.41	-1	1	1	0.002
9.91	24	8.92	0	0	2	0.003
10.41	18	8.49	0	2	0	0.024
11.18	24	7.91	2	0	0	0.038
11.63	41	7.60	-1	1	2	0.003
12.37	59	7.15	-1	2	1	-0.003
13.19	6	6.71	1	2	1	-0.014
13.45	3	6.58	-2	0	2	0.007
14.05	6	6.30	2	1	1	0.011
14.38	6	6.16	0	2	2	0.003
14.71	10	6.02	-1	2	2	-0.008
15.26	13	5.80	2	2	0	0.001
15.76	10	5.62	-1	1	3	0.008
16.09	1	5.51	1	2	2	-0.010
16.32	1	5.43	2	0	2	0.035
16.69	4	5.31	2	2	1	-0.007
17.03	3	5.20	-1	3	1	0.026
17.63	6	5.03	1	3	1	0.006
18.17	5	4.88	-1	2	3	-0.004
18.78	7	4.72	-1	3	2	-0.014
19.30	1	4.60	-2	3	1	-0.019
19.61	2	4.52	-3	2	1	0.036
19.86	20	4.47	-2	2	3	0.040
20.29	10	4.37	2	0	3	0.019
20.57	4	4.31	0	1	4	0.006
21.12	1	4.20	3	0	2	0.048
21.57	12	4.12	-2	1	4	0.028
22.46	10	3.96	1	4	1	0.035

2 Θ [°]	intensity I/I_o [%]	d_{hkl} [Å]	labelling h	k	l	$d_{exp-calc}$ [Å]
23.03	35	3.86	4	1	0	0.022
23.39	21	3.80	-1	4	2	0.019
24.08	2	3.69	-3	1	4	-0.006
24.51	1	3.63	-4	0	3	0.036
24.91	10	3.57	-2	4	2	0.003
25.14	39	3.54	3	1	3	0.043
25.69	36	3.47	-3	3	3	0.041
26.68	3	3.34	0	5	1	0.035
26.90	2	3.31	3	4	0	0.027
27.10	2	3.29	0	2	5	0.030
27.42	3	3.25	4	3	0	0.006
28.19	2	3.16	-1	5	2	-0.035
28.54	2	3.12	3	0	4	0.047
28.94	11	3.08	0	4	4	-0.036
29.18	5	3.06	-4	3	3	0.017
29.50	4	3.03	-1	0	6	0.041
30.18	7	2.96	-1	5	3	-0.042

Table 2: Lattice metrics of the anhydrous form A

Symmetry:	monocline
spatial group:	P
a:	16.16(2) Å
b:	17.02(1) Å
c:	18.18(2) Å
ß:	100.95(6) °
cell volume:	4907(11) $Å^3$

5

Example 2 **Crystallisation of polymorph B**

Polymorph B is obtained by cooling form A from Example 1 to temperatures <10 °C.

Table 3: Labelled X-ray reflexes up to 30 ° 2 Θ with intensities (standardised) for the anhydrous form B

2 Θ [°]	intensity I/I_o [%]	d_{hkl} [Å]	labelling h	k	l	$d_{exp-calc}$ [Å]
5.82	3	15.17	1	0	0	-0.007
7.04	33	12.55	0	1	1	0.001
7.82	100	11.3	1	1	0	-0.004
8.84	11	10	-1	1	1	0.001
9.44	40	9.36	1	1	1	0.011
10.62	14	8.32	-1	0	2	0.013
10.79	24	8.19	0	1	2	-0.005
11.82	39	7.48	-1	1	2	-0.003
12.64	53	7	-1	2	1	-0.009
13.07	11	6.77	1	2	1	-0.006
13.24	6	6.68	-2	1	1	0.004
14.04	16	6.3	2	1	1	0.003
15.23	17	5.81	-2	1	2	0.003
15.70	22	5.64	2	2	0	0.016
16.38	2	5.41	0	3	1	-0.010
16.73	6	5.3	2	2	1	0.008
17.67	8	5.02	0	2	3	0.014
18.16	3	4.88	-1	2	3	0.005
18.33	9	4.84	3	1	0	0.016
18.48	10	4.8	-3	1	1	-0.003
18.97	15	4.68	0	0	4	-0.001
19.56	6	4.54	1	3	2	0.013

2 Θ [°]	intensity I/I$_o$ [%]	d_{hkl} [Å]	labelling h	k	l	$d_{exp-calc}$ [Å]
20.00	17	4.44	2	1	3	0.000
20.42	9	4.35	1	0	4	0.009
20.76	4	4.27	3	0	2	-0.014
20.97	4	4.23	0	4	0	0.010
21.07	5	4.21	1	1	4	-0.009
21.22	12	4.18	0	3	3	0.001
21.40	7	4.15	3	2	1	0.004
21.66	4	4.1	-1	3	3	0.018
21.98	7	4.04	2	2	3	-0.003
22.16	10	4.01	-3	1	3	0.008
22.97	3	3.87	1	2	4	-0.006
23.58	43	3.77	-2	3	3	-0.003
23.78	15	3.74	-2	2	4	-0.004
24.05	6	3.7	4	1	0	-0.002
24.29	8	3.66	-2	4	1	-0.008
24.46	5	3.64	3	3	1	0.018
24.71	7	3.6	0	3	4	0.001
24.96	23	3.56	2	3	3	-0.001
25.45	12	3.5	-2	4	2	-0.010
25.75	35	3.46	4	2	0	0.011
25.99	4	3.43	3	2	3	0.014
26.15	6	3.41	3	3	2	0.010
26.57	12	3.35	-2	3	4	-0.001
26.82	4	3.32	-3	2	4	0.011
27.20	6	3.28	1	2	5	-0.010
27.43	4	3.25	-2	4	3	-0.003
27.60	3	3.23	-2	2	5	-0.005
28.19	4	3.16	3	4	1	0.010
28.40	15	3.14	0	4	4	-0.013
28.64	12	3.11	0	0	6	0.016

2 Θ [°]	intensity I/I$_o$ [%]	d_{hkl} [Å]	labelling h	k	l	$d_{exp-calc}$ [Å]
29.18	6	3.06	-4	3	2	0.004
29.42	2	3.03	1	4	4	0.002
29.99	10	2.98	0	5	3	-0.008
30.77	3	2.9	-4	3	3	0.018

Table 4: Lattice metrics of the anhydrous form B

Symmetry:	monocline
spatial group:	$P2_1/c$ (# 14)
a:	15.23(1) Å
b:	16.94(1) Å
c:	18.79(1) Å
ß:	95.6(2) °
cell volume:	4823(3) Å^3

Example 3 **Crystallisation of polymorph C**

Crude 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(*R*)-amino-piperidin-1-yl)-xanthine (26 kg) is refluxed with 157 l methanol, combined with 1.3 kg of activated charcoal and after 30 minutes' stirring the mixture is filtered and rinsed with 26 l methanol. 122 l of methanol are distilled off from the filtrate, then the residue is cooled to 45-55°C. 52 l of tert.-butylmethylether are added to the residue over 30 minutes. Then the mixture is stirred for another 60 minutes at 45-55°C. Crystallisation takes place within this time. A further 78 l tert. butylmethylether are added to the suspension over 30 minutes and then it is stirred again for a further 60 minutes at 45-55°C. It is diluted to four times the volume. The suspension is slowly cooled to 15-25°C and stirred overnight at this temperature. After the suspension has been cooled to 0-5°C the crystals are suction filtered, washed with 2 batches tert.-butylmethylether and dried at 70°C in the vacuum dryer.

Table 5: X-ray reflexes up to 30 ° 2 Θ with intensities (standardised) for the anhydrous form C

2 Θ [°]	d_{hkl} [Å]	intensity I/I_o [%]
3.38	26.16	4
6.85	12.90	100
7.18	12.31	11
7.52	11.74	14
7.96	11.10	36
9.80	9.02	3
11.11	7.96	2
11.58	7.64	3
12.30	7.19	5
13.30	6.65	16
13.75	6.44	26
14.38	6.16	17
14.74	6.01	11
14.95	5.92	10
15.63	5.66	6
16.28	5.44	5
17.81	4.98	10
18.33	4.83	6
18.75	4.73	15
20.51	4.33	8
20.77	4.27	8
21.47	4.14	3
21.96	4.05	4
22.59	3.93	26
23.76	3.74	29
24.68	3.60	6
25.01	3.56	7
25.57	3.48	4
25.96	3.43	4
26.93	3.31	18
27.22	3.27	13
27.92	3.19	10

Example 4 **Crystallisation of polymorph D**

Polymorph C is obtained if polymorph C from Example 3 is heated to a temperature of 30-100°C or dried at this temperature.

Example 5 **Crystallisation of polymorph E**

Anhydrous polymorph E is obtained if polymorph D is melted. On further heating, polymorph E crystallises out of the melt.

In the DSC diagram of form C a whole range of signals can be observed. The strongest signal is the melting point of the anhydrous form A at approx. 206 °C, which is produced in the DSC experiment. Before the melting point a number of other endothermic and exothermic signals can be observed. Thus, for example, a very broad and weak endothermic signal can be seen between 30 and 100°C, which correlates with the main loss of weight in thermogravimetry (TR). A TG/IR coupling

experiment provides the information that only water escapes from the sample in this temperature range.

An X-ray powder diagram taken of a sample maintained at a temperature of 100°C shows different X-ray reflexes from the starting material, suggesting that form C is a hydrate phase with stoichiometry somewhere in the region of a hemihydrate or monohydrate. The temperature-controlled sample is another anhydrous modification D, which only stable under anhydrous conditions. The D form melts at approx. 150°C. Another anhydrous crystal modification E crystallises from the melt, and when heated further melts at approx. 175 °C. Finally, form A crystallises from the melt of form E. Form E is also a metastable crystal modification which occurs only at high temperatures.

CLAIMS:

1. A method of preparing anhydrous polymorph B of the compound 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine, characterised in that at a temperature of 10-40°C it transforms reversibly into the polymorph A,
wherein polymorph B is prepared by
(a) dissolving 1-[(4-methyl-quinazolin-2-yl)methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine in absolute ethanol and refluxing and optionally filtering the mixture,
(b) cooling the hot solution or the hot filtrate for crystallisation to a temperature below 10°C,
(c) diluting with a solvent,
(d) suction filtering the solvent mixture and
(e) drying the polymorph at a temperature below 10°C *in vacuo*;
or by cooling anhydrous polymorph A or a mixture of polymorphs A and B to temperatures <10°C,

wherein anhydrous polymorph A is characterised in that it melts at 206±3 °C or in that in the X-ray powder diagram it has inter alia characteristic reflexes at the following d values: 11.59 Å, 7.60 Å, 7.15 Å, 3.86 Å, 3.54 Å and 3.47 Å.

2. Method according claim 1, wherein polymorph B is characterised in that in the X-ray powder diagram it has *inter alia* characteristic reflexes at the following d values: 11.3 Å, 9.36 Å, 7.48 Å, 7 Å and 3.77 Å.

3. The method according claim 1 or 2, wherein the X-ray powder diagram of polymorph B is substantially free of the characteristic reflexes of polymorph A at the following d values: 11.59 Å, 7.60 Å, 7.15 Å, 3.86 Å, 3.54 Å and 3.47 Å.

4. The method according to claim 1, 2 or 3, wherein polymorph B is characterised by the following lattice metrics:

Symmetry:	monocline
spatial group:	$P2_1/c$ (# 14)
a:	15.23(1) Å
b:	16.94(1) Å
c:	18.79(1) Å
ß:	95.6(2) °
cell volume:	4823(3) $Å^3$

5. The method according claim 1, 2, 3 or 4, wherein the X-ray powder diagram of polymorph B is as shown in Figure 4.

6. The method according to claim 1, 2, 3, 4 or 5, wherein the solvent is tert.-butylmethylether.

Figures:

Figure 1: Thermoanalysis of the anhydrous form A/B

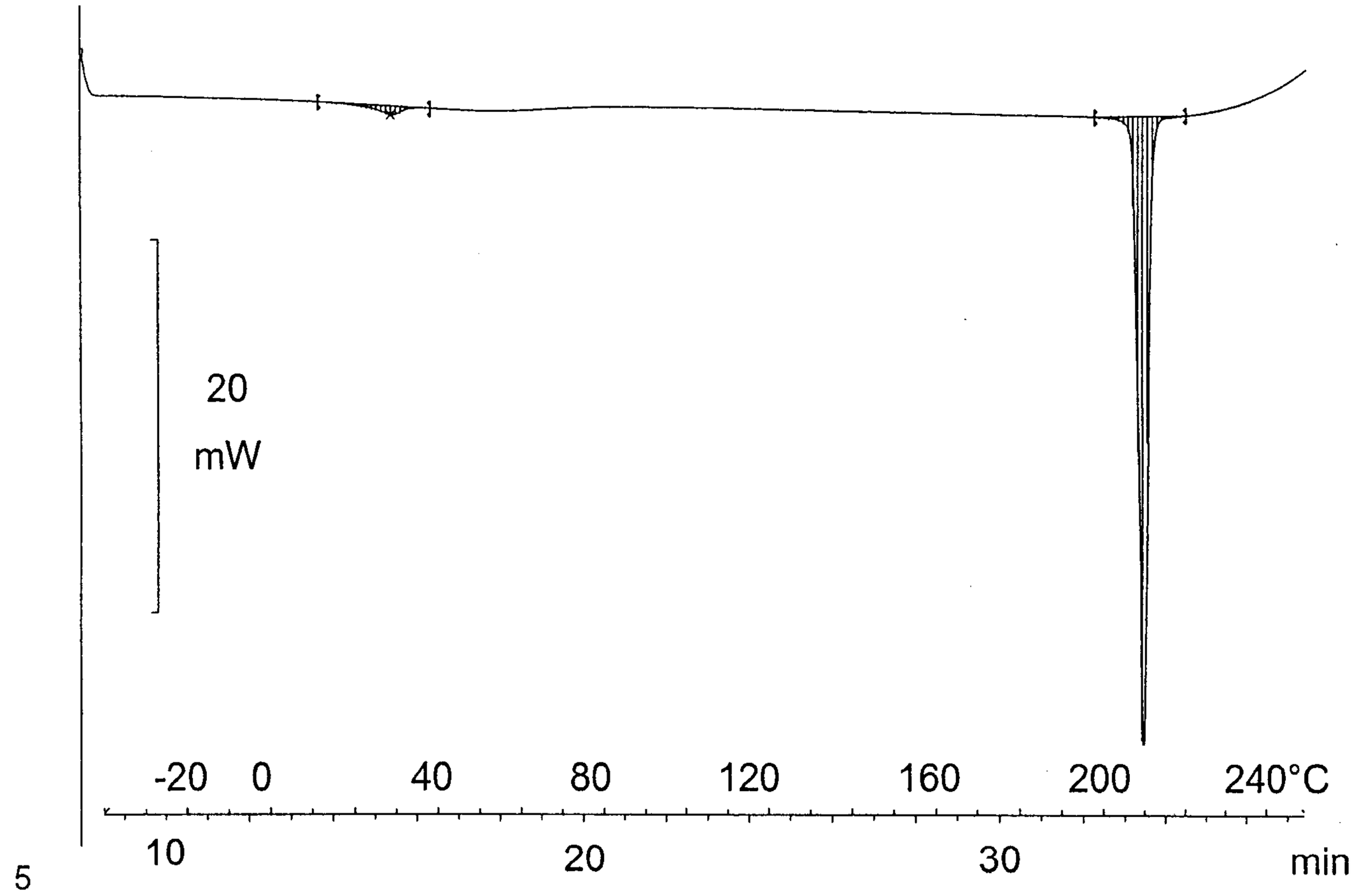

Figure 2: Cyclic DSC diagram of the enantiotropic phase transition

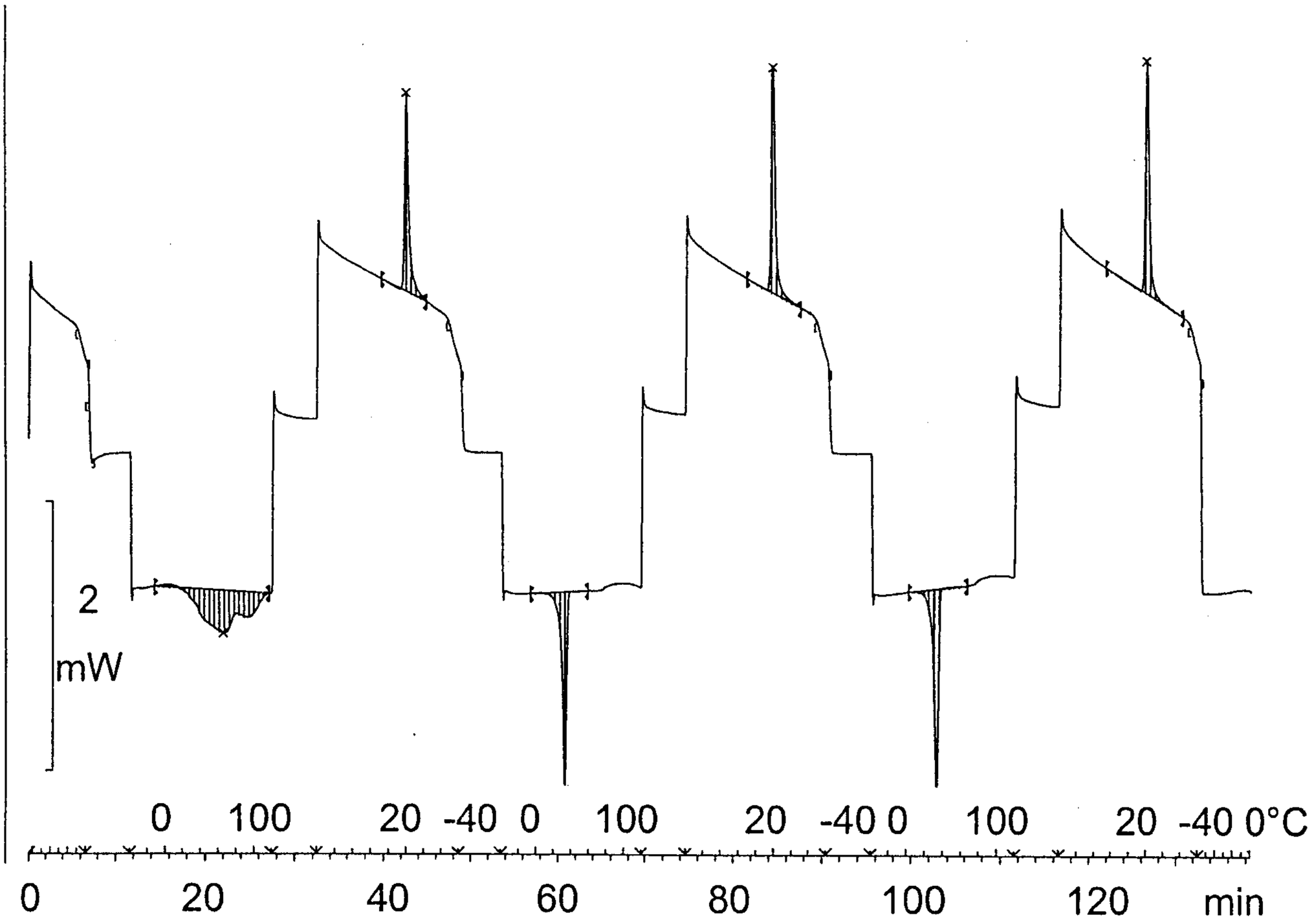

Figure 3: X-ray powder diagram of the anhydrous form A

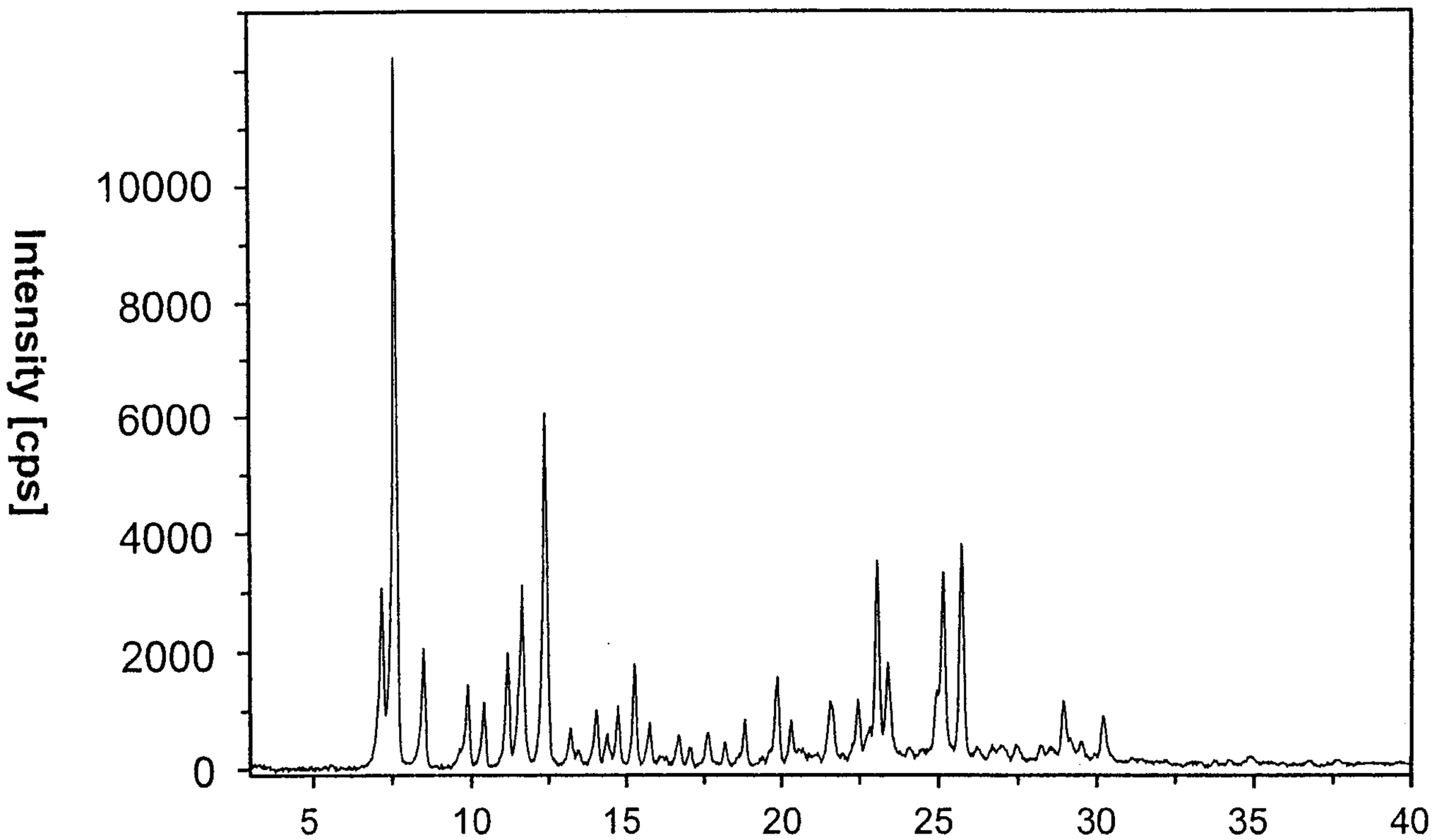

Figure 4: X-ray powder diagram of the anhydrous form B

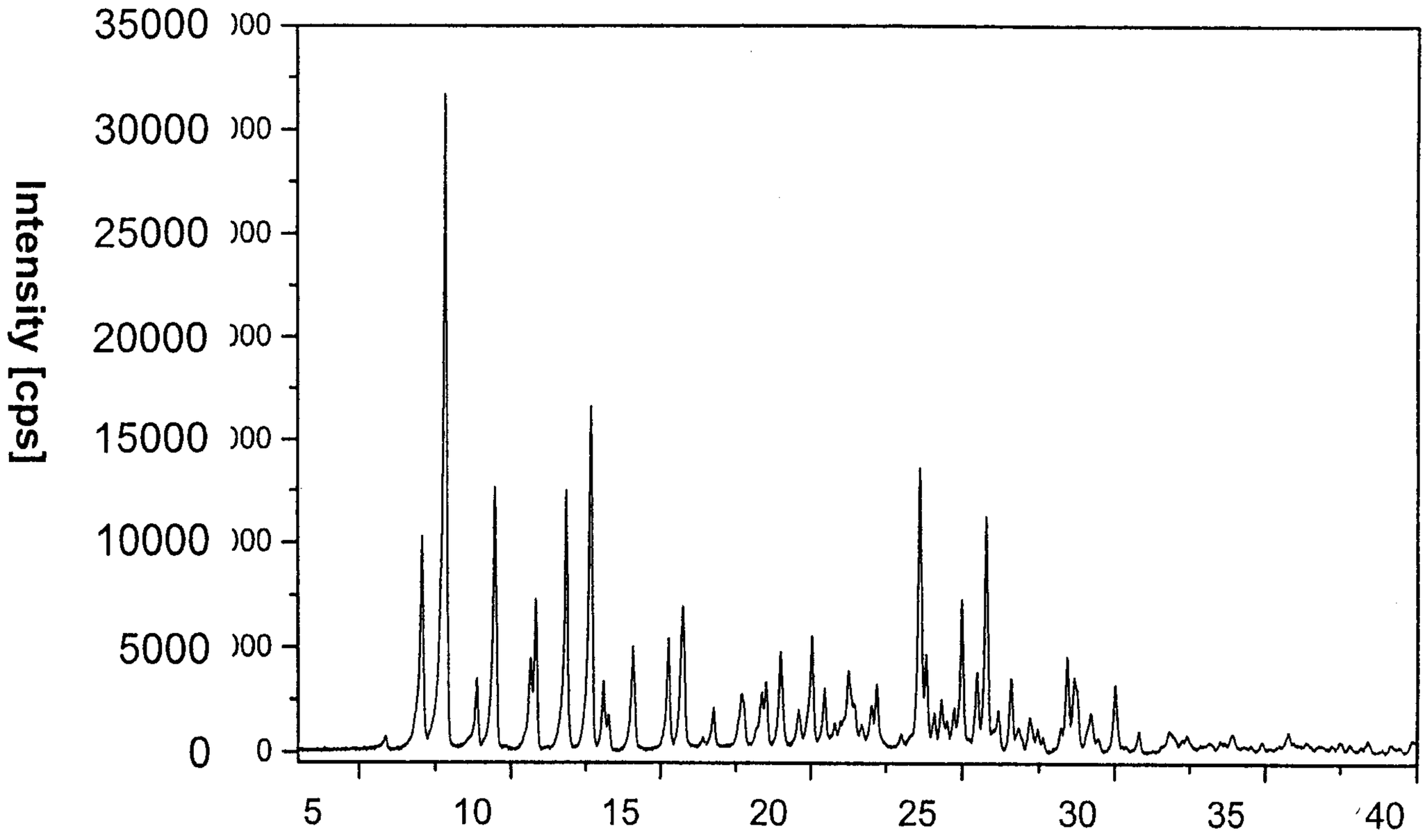

Figure 5: X-ray powder diagram of polymorph C

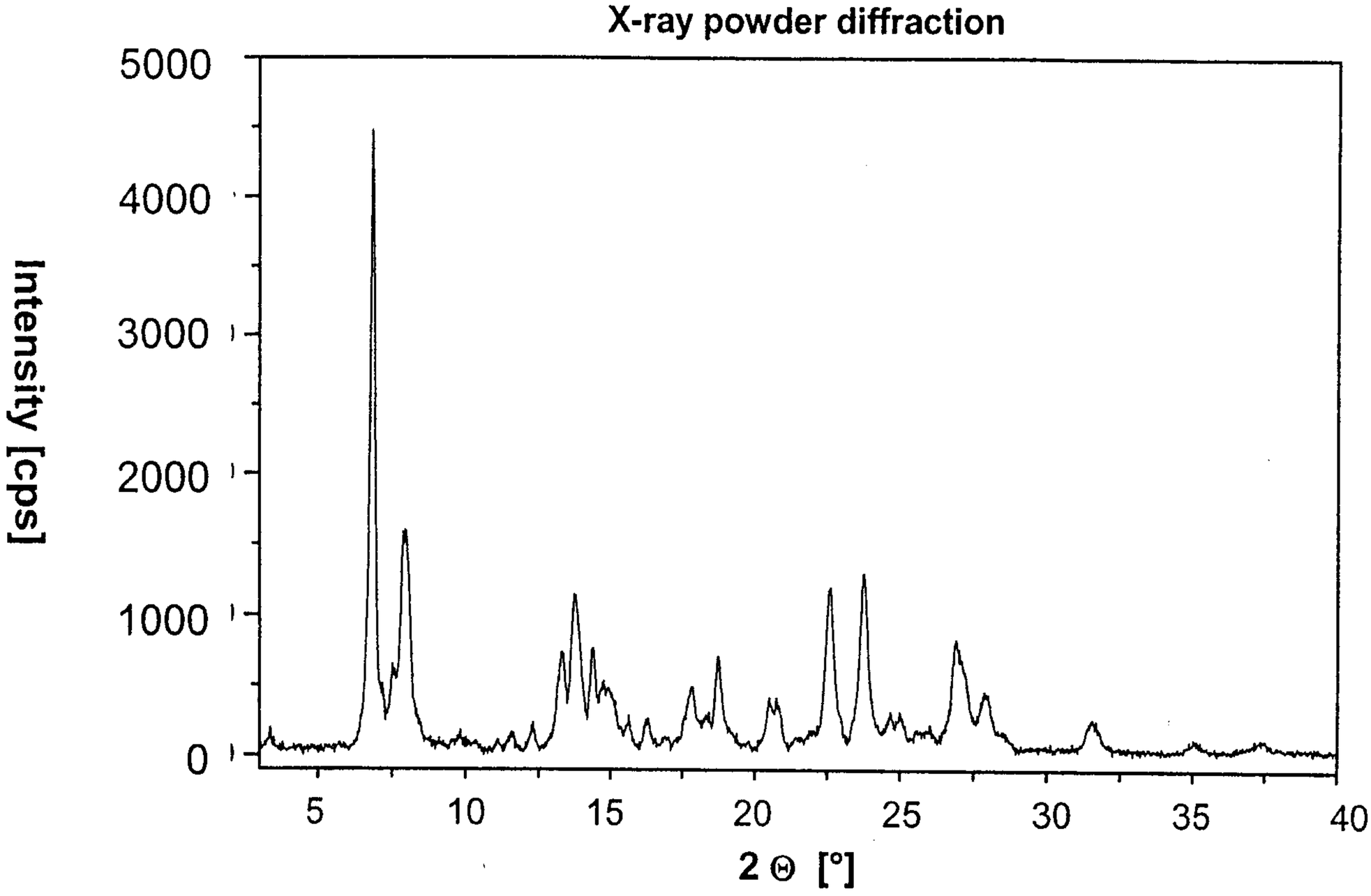

Figure 6: Thermoanalysis of form C