



## Thermodynamic relationships between nateglinide polymorphs

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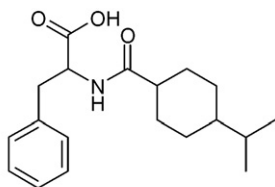
### ABSTRACT

The physico-chemical characterization of the polymorphs of nateglinide (named B, H and S), an antidiabetic agent, has been performed by means of thermal, diffractometric, spectroscopic and electron microscopic measurements. It has been established that S polymorph can crystallize from the melt obtained from both B and H samples or also following an isothermal treatment of both forms at temperatures lower than the relevant melting points. By X-ray diffraction it could be shown that the three polymorphs have different crystal structure. On the other hand the indication has been drawn from IR spectra that the molecular structure of B is sensibly different from those of H and S forms that have a very similar molecular structure. Finally, the microstructure features of the three polymorphs have been examined by scanning electron microscopy. Our analyses have allowed to evaluate the relative stability of the three polymorphs through the construction of the energy vs. temperature diagram. In particular, S polymorph, the highest-melting form, has resulted to be the only stable form, while the B and H forms are metastable.

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### 1. Introduction

Nateglinide, (–)-N-[(trans-4-isopropylcyclohexane carbonyl)-D-phenylalanine], is an oral antidiabetic drug [1] used in the treatment of Type 2 diabetes. The drug exert a stimulating effect on the insulin secretion from pancreatic beta cells so lowering the blood sugar level.



Structural formula of nateglinide

At the moment, in addition to several solvate forms, three polymorphs, named B, H and S, are known for nateglinide [2] but no thermodynamic data are available. The topic of this paper has been the physico-chemical characterization of nateglinide with particular care to the thermodynamic relationship between the various polymorphs in which it can exist and to the ways of their interconversion. In fact in the pharmaceutical field the importance of identifying the lowest energy crystalline polymorph of a drug is widely admitted [3–5] since such a form will be the most chemi-

cally stable one and it will not convert to another polymorph during storage. For the investigation of the nateglinide polymorphism we have used a variety of techniques (thermal methods, X-ray diffraction, FTIR spectroscopy and scanning electron microscopy). We have been able to assess the thermodynamic stability relationships of polymorphs on the basis of thermodynamic rules according to Burger and Ramberger [6] and by energy vs. temperature diagrams which allow to distinguish between monotropic and enantiotropic system and to calculate the potential transition temperature [7]. Furthermore, the differences between the polymorphs have been revealed as concerns structural, microstructural and molecular aspects.

### 2. Materials and methods

Nateglinide polymorphs B and H came from R&D samples (AMSA S.p.A., Como, Italy).

Thermal analyses were carried out with a TGA Q5000 IR apparatus and a DSC Q2000 apparatus both interfaced with a TA 5000 data station (TA Instruments, USA). Thermogravimetric curves were recorded at 3 K min<sup>-1</sup>, in a standard open platinum holder, under a flow of nitrogen (3 L h<sup>-1</sup>). The DSC instrument was calibrated using ultrapure (99.999%) indium (m.p. = 156.6 °C; ΔH = 28.54 J g<sup>-1</sup>) as standard. The calorimetric measurements were conducted with sealed standard aluminum pans under a flow of nitrogen (3 L h<sup>-1</sup>) at different heating rate (0.5–20 K min<sup>-1</sup>). All numeric figures from thermal measurements are averages of three or more experiments.

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FTIR spectra by diffuse reflectance were obtained with a Nicolet FT-IR 730 Spectrometer equipped with a DRIFT collector by Spectra Tech, UK. Samples were thoroughly mixed with anhydrous KBr and the spectra were collected by co-adding 1024 scans in the 4000–400  $\text{cm}^{-1}$  range at 4  $\text{cm}^{-1}$  resolution.

X-ray diffraction patterns ( $\text{CuK}\alpha$  radiation; voltage of 40 kV and current of 30 mA) were collected with a powder diffractometer Bruker D5005 (Siemens, Germany) equipped with a  $\theta$ – $\theta$  vertical goniometer and a Position Sensitive Detector (PSD, Braun). The spectra have been recorded in the step scan mode (step: 0.015°; counting time: 0.5 s) in the angular range  $2\theta=5$ –30° with a polythermal chamber at controlled temperature.

SEM microphotographs were collected on gold-sputtered samples with a Cambridge Stereoscan 200 Scanning Electron Microscopy.

### 3. Results and discussion

#### 3.1. B sample

##### 3.1.1. TG measurements

B sample does not show any appreciable mass change up to 160 °C when it begins slowly to decompose.

##### 3.1.2. DSC measurements

**3.1.2.1. Single runs.** As it is evident from Fig. 1, the thermal behaviour of B polymorph is a function of the heating rate ( $\beta$ ). In particular, the DSC run at 0.5  $\text{K min}^{-1}$  shows an endo–exothermic effect, with an onset at about 128 °C followed by an endothermic peak at 172 °C. With increasing  $\beta$  the separation between the endothermic and the exothermic effects takes place. While the endothermic peak is always present at the same temperature values, the exothermic effect moves to high temperature up to disappear with  $\beta \geq 10 \text{ K min}^{-1}$ . With these heating rates the endothermic peak at 172 °C is missing as well. Quantitative data measured at different  $\beta$  are reported in Table 1 from which it can be observed that:

- The onset temperature ( $T_{e,1}$ ) and the enthalpy change ( $\Delta H_1$ ) of the first endothermic peak (except for the measurement performed at 0.5  $\text{K min}^{-1}$  in which a reliable peak integration is not possible) and the enthalpy change of the exothermic peak ( $\Delta H_{\text{exo}}$ ) do not depend on  $\beta$ .
- The enthalpy change of the exothermic peak overlaps as absolute value, within the experimental error, with that of the endothermic peak at 172 °C ( $\Delta H_2$ ).

**3.1.2.2. Cyclic measurements.** In order to evaluate the reversible character of the thermal events, cyclic measurements have been performed as follows:

- first heating at 2  $\text{K min}^{-1}$  up to 133 °C (temperature corresponding to the first endothermic peak end) or up to 150 °C (temperature corresponding to the exothermic peak end);

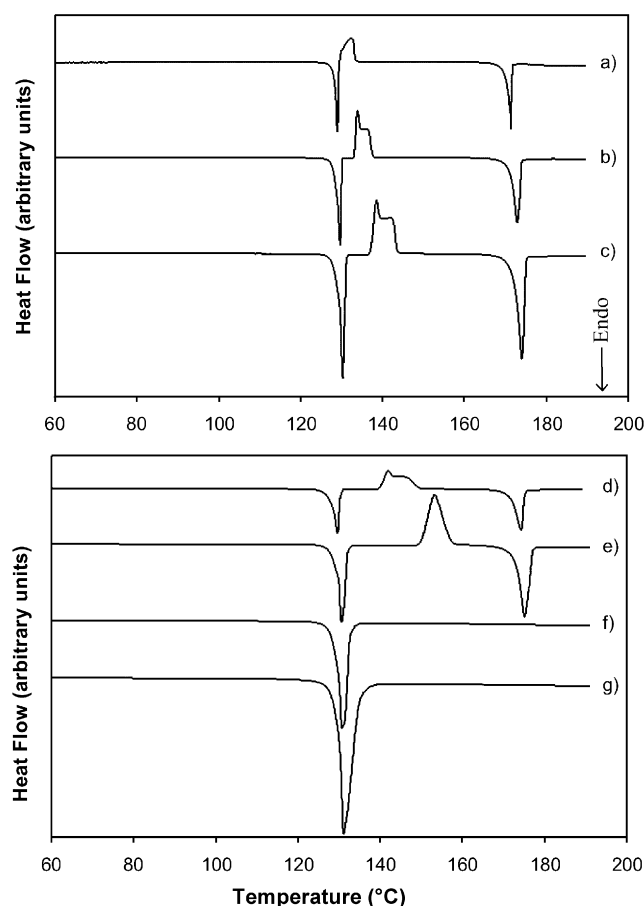


Fig. 1. DSC curves of B sample at different heating rates: 0.5  $\text{K min}^{-1}$  (curve a), 1  $\text{K min}^{-1}$  (curve b), 2  $\text{K min}^{-1}$  (curve c), 3  $\text{K min}^{-1}$  (curve d), 5  $\text{K min}^{-1}$  (curve e), 10  $\text{K min}^{-1}$  (curve f) and 20  $\text{K min}^{-1}$  (curve g).

- cooling down to room temperature;
- second heating to 200 °C.

When the temperature reached in the first heating is 133 °C, during cooling an exothermic peak is recorded at once with a size corresponding to that of the exothermal peak present in a single run. On the contrary, when the temperature reached in the first heating is 150 °C, during cooling no thermal event is present. In the second heating, independently from the temperature reached in the first ramp, an endothermic peak, that can be superimposed to that present at 172 °C in a single run, is always recorded.

**3.1.2.3. Isothermal measurements.** Measurements with an isothermal step of 12 or 24 h have been carried out on B polymorph at different temperatures which precede the sample melting: 105 °C, 110 °C, 114 °C and 116 °C. As it can be seen in Table 2, the annealing

Table 1

Quantitative data from thermal measurements on B sample at different heating rates.

$\beta$ ( $\text{K min}^{-1}$ )	$T_{e,1}$ (°C)	$\Delta H_1$ ( $\text{J g}^{-1}$ )	$T_{e,\text{exo}}$ (°C)	$\Delta H_{\text{exo}}$ ( $\text{J g}^{-1}$ )	$T_{e,2}$ (°C)	$\Delta H_2$ ( $\text{J g}^{-1}$ )
0.5	128.3	Not reliable	–	Not reliable	171.6	99.2
1	128.6	83.2	133.2	–98.4	171.4	99.6
2	129.4	82.0	137.2	–100.4	172.2	102.3
3	129.3	87.3	140.5	–101.3	173.2	102.6
5	129.8	86.1	150.1	–101.6	172.9	102.4
10	129.5	85.9	–	–	–	–
20	129.8	88.4	–	–	–	–
Mean value $\pm$ s.d.	129.2 $\pm$ 0.6	85.5 $\pm$ 2.4	–	–100.4 $\pm$ 1.4	172.2 $\pm$ 0.9	101.2 $\pm$ 1.5

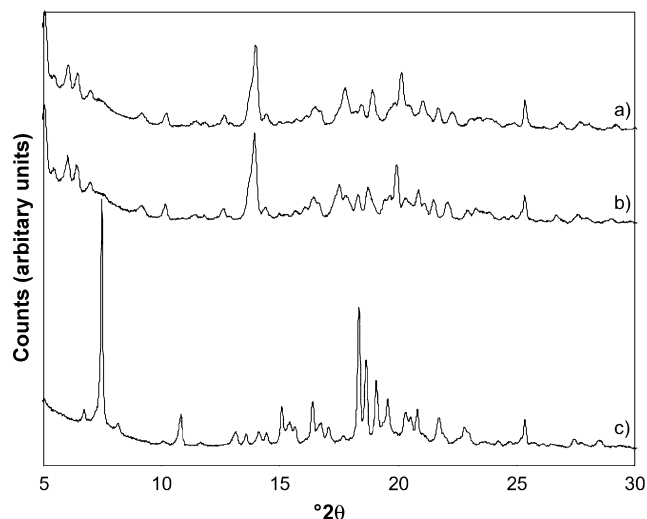
**Table 2**  
Quantitative data obtained with B sample after the isothermal step at different temperature and time.

Isothermal $T$ and $t$	$T_{e,1}$ ( $^{\circ}\text{C}$ )	$\Delta H_1$ ( $\text{J g}^{-1}$ )	$T_{e,exo}$ ( $^{\circ}\text{C}$ )	$\Delta H_{exo}$ ( $\text{J g}^{-1}$ )	$T_{e,2}$ ( $^{\circ}\text{C}$ )	$\Delta H_2$ ( $\text{J g}^{-1}$ )
105 $^{\circ}\text{C}$ 12 h	128.6	89.3	148.1	-99.4	173.3	103.2
105 $^{\circ}\text{C}$ 24 h	128.2	87.3	139.5	-96.3	173.0	104.7
110 $^{\circ}\text{C}$ 24 h	127.9	59.6	139.3	-58.3	174.2	106.4
114 $^{\circ}\text{C}$ 24 h	127.7	2.0	136.7	-2.0	174.6	106.5
116 $^{\circ}\text{C}$ 12 h	127.8	9.4	139.0	-6.5	174.8	106.5
116 $^{\circ}\text{C}$ 12 h	-	-	-	-	174.9	109.2
Mean value $\pm$ s.d.					174.1 $\pm$ 0.8	106.1 $\pm$ 2.0

at 105  $^{\circ}\text{C}$  does not affect the thermal behaviour of the sample in the subsequent ramp. On the contrary, with increasing the isothermal step temperature and time, the enthalpy changes of the peak at 128  $^{\circ}\text{C}$  ( $\Delta H_1$ ) and of the exothermic peak ( $\Delta H_{exo}$ ) become lower. These two effects are missing after 24 h at 116  $^{\circ}\text{C}$ . The enthalpy change of the peak at 172  $^{\circ}\text{C}$  ( $\Delta H_2$ ) is constant at 106.1  $\pm$  2.0  $\text{J g}^{-1}$ . This value is lightly higher than the one measured for the same peak in runs not preceded by isothermal step (101.2  $\pm$  1.5).

**3.1.2.4. Discussion of DSC measurements.** The experimental picture here described is compatible with the following model: at low  $\beta$  the B polymorph melts at 129  $^{\circ}\text{C}$  and a new polymorph is formed which melts at 172  $^{\circ}\text{C}$ . The crystallization of the new solid form is a relatively slow kinetics process which does not occur at high  $\beta$ : this is the reason why, with  $\beta \geq 10 \text{ K min}^{-1}$  other thermal events, in addition to the one at 129  $^{\circ}\text{C}$ , are not present. In literature [2] the existence of a polymorph of nateglinide named S which melts at about 170  $^{\circ}\text{C}$  is reported. We believe that what crystallizes during heating of the melt at relatively low  $\beta$  is just the S polymorph.

DSC cyclic measurements suggest that the S form is obtained from cooling of melt as well. From DSC measurements with isothermal step at temperature lower than the sample melting we can infer that the annealing of B polymorph at temperature of at least 110  $^{\circ}\text{C}$  causes the polymorphic transition in solid phase to S form. The fact that the melting enthalpy of S form is slightly higher than the one measured in a run with no annealing suggests that in the original B sample a limited portion of amorphous nateglinide is present. The annealing at high temperature for enough time allows nateglinide crystallization. Therefore, we think that the correct value of melting enthalpy of S form is the one measured after the isothermal step (106.1  $\pm$  2.0  $\text{J g}^{-1}$ ) rather than the one measured in a single run. The

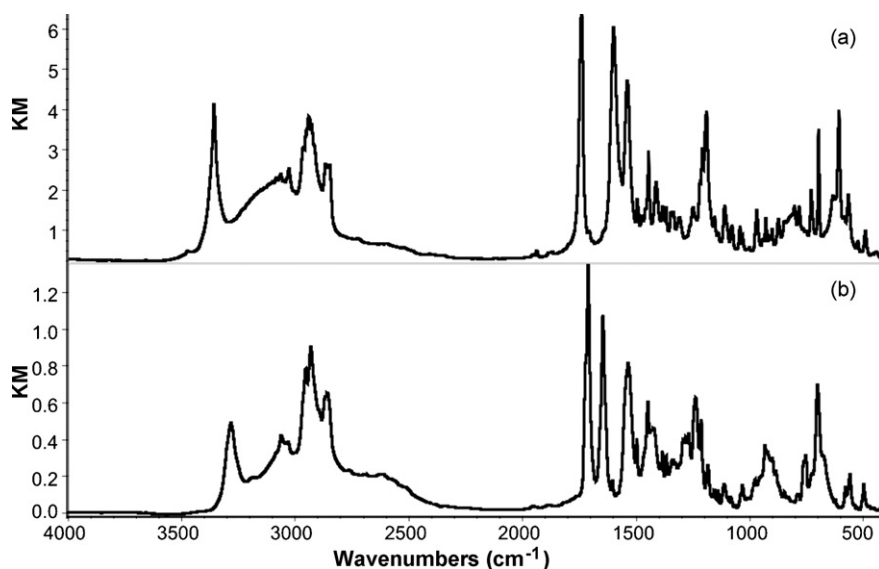


**Fig. 2.** X-ray patterns of B sample at different temperatures: room temperature (curve a), 110  $^{\circ}\text{C}$  (curve b) and 140  $^{\circ}\text{C}$  (curve c).

amorphous portion present in the original sample is 4.6% by mass. In the same way, the enthalpy change we measured for the B polymorph has to be corrected taking into account the presence of this amorphous portion to 89.6  $\text{J g}^{-1}$ .

### 3.1.3. X-ray measurements

Fig. 2 shows the X-ray powder pattern of B sample (trace a). The pattern of the sample heated at 2  $\text{K min}^{-1}$  up to 110  $^{\circ}\text{C}$  (temperature lower than the melting point, trace b) does not show significant



**Fig. 3.** FTIR spectra of B sample: original (curve a) and heated to 150  $^{\circ}\text{C}$  (curve b).

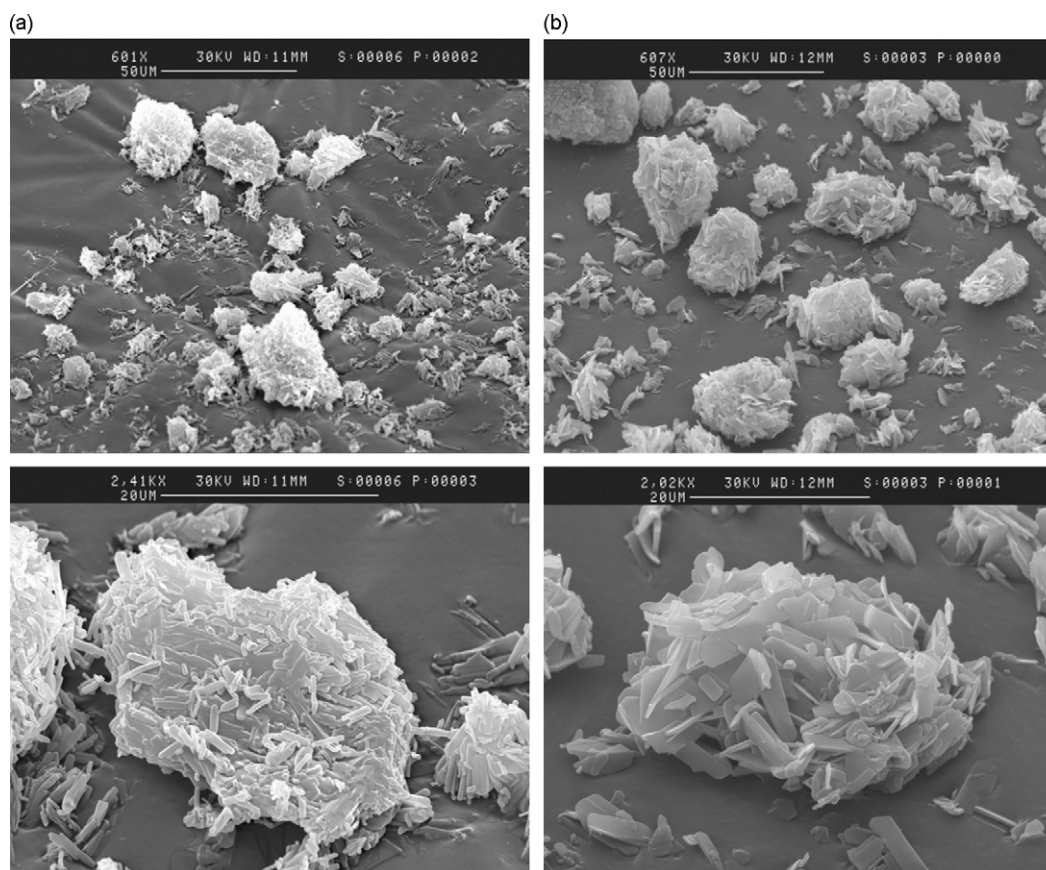


Fig. 4. SEM micrographs of B sample: original (column a) and annealed 24 h at 116 °C (column b).

variations with respect to that of B sample. On the contrary the pattern of the sample heated up to 140 °C (temperature corresponding to the exothermic peak, trace c), is definitely different and this confirms the formation of a new crystalline form.

#### 3.1.4. FTIR measurements

The FTIR measurements show (Fig. 3) that the spectra of sample B heated at 2 K min<sup>-1</sup> up to 150 °C (temperature corresponding to the closing of exothermic peak) is (trace b) the same as that of the B form annealed 24 h at 116 °C and that these spectra are significantly different from the one of the original B sample (trace a). The main differences are as follows:

- (i) the stretching of the NH group is at 3357 cm<sup>-1</sup> (spectrum a) while it is at 3282 cm<sup>-1</sup> in spectrum b;
- (ii) the stretching of the amide carbonyl group (amide band I) in spectrum a is located at a wavenumber (1600 cm<sup>-1</sup>) that falls below the reference range (1675 ± 30 cm<sup>-1</sup>) while it is located within the reference range in spectrum b (1646 cm<sup>-1</sup>);
- (iii) the stretching of carbonyl group of the carboxylic function is at 1741 cm<sup>-1</sup> (spectrum a) and at 1710 cm<sup>-1</sup> (spectrum b);
- (iv) the broad band of the in plane deformation of OH group is at 1412 cm<sup>-1</sup> (spectrum a) and at 1448 cm<sup>-1</sup> (spectrum b);
- (v) the stretching of C–O group is at 1190 cm<sup>-1</sup> (spectrum a) while it shows up as a multiple band (1267–1241–1213 cm<sup>-1</sup>) in the spectrum b.

In particular the spectral remarks under points (i), (ii) and (iii) could be explained on the basis of a different pattern of hydrogen bonds: in the B form both the NH (amide) and C=O (carboxyl) groups seem to be free from H-bonds while it is the C=O (amidic) group that appears to be engaged in these bonds. The opposite is true in the

spectrum of the heated sample. Thus the IR spectra show that the molecular structure of the B form transforms when it is annealed for 24 h at 116 °C.

Therefore, the model suggested for the interpretation of DSC measurements is confirmed both from FTIR and from X-ray measurements.

#### 3.1.5. SEM measurements

SEM micrographs of original B sample and of B sample annealed 24 h at 116 °C are shown in Fig. 4. The original B polymorph is made of sticks of some μm in length in most cases melted to form blocks. As a consequence of the annealing a particle enlargement is produced. In particular, a growth mainly along one axis takes place so that the particles acquire a flat shape.

### 3.2. H sample

#### 3.2.1. TG measurements

The H polymorph does not have mass losses below 160 °C.

#### 3.2.2. DSC measurements

3.2.2.1. *Single runs.* As for B sample, DSC traces of H polymorph too change with β. The DSC curve at 0.5 K min<sup>-1</sup> (Fig. 5) shows an endo-exothermic effect, with onset temperature at about 137 °C, followed by an endothermic peak at 173 °C. With increasing β, the separation between the endothermic and the exothermic effects is produced. While the endothermic peak always occurs at the same temperature, the exothermic effect shifts to higher temperature up to disappear with β ≥ 10 K min<sup>-1</sup>. At these heating rates also the endothermic peak at 173 °C is absent. Quantitative data recorded at different β are reported in Table 3:

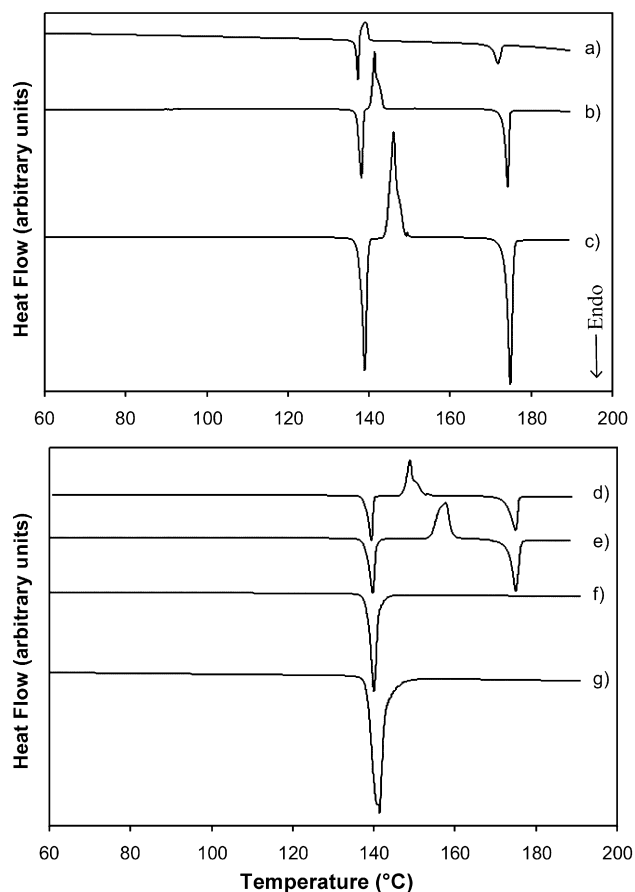


Fig. 5. DSC curves of H sample at different heating rates: 0.5 K min<sup>-1</sup> (curve a), 1 K min<sup>-1</sup> (curve b), 2 K min<sup>-1</sup> (curve c), 3 K min<sup>-1</sup> (curve d), 5 K min<sup>-1</sup> (curve e), 10 K min<sup>-1</sup> (curve f) and 20 K min<sup>-1</sup> (curve g).

- the onset temperature ( $T_{e,1^*}$ ) and the enthalpy change ( $\Delta H_{1^*}$ ) of the first endothermic peak (except for the measurement at 0.5 K min<sup>-1</sup> in which the missing resolution between the endo and the exothermic effects does not allow a reliable integration) and the enthalpy change of the exothermic peak ( $\Delta H_{exo^*}$ ) are independent of  $\beta$ ;

Table 3

Quantitative data from thermal measurements on H sample at different heating rates.

$\beta$ (K min <sup>-1</sup> )	$T_{e,1^*}$ (°C)	$\Delta H_{1^*}$ (J g <sup>-1</sup> )	$T_{e,exo^*}$ (°C)	$\Delta H_{exo^*}$ (J g <sup>-1</sup> )	$T_{e,2^*}$ (°C)	$\Delta H_{2^*}$ (J g <sup>-1</sup> )
0.5	136.8	Not reliable	–	Not reliable	173.2	105.9
1	136.9	95.6	140.5	–100.6	173.2	105.9
2	137.8	97.2	144.4	–99.2	173.7	103.2
3	138.0	94.5	147.4	–98.3	172.4	101.3
5	138.0	96.1	154.1	–100.0	173.2	104.5
10	138.4	96.5	–	–	–	–
20	138.3	97.6	–	–	–	–
Mean value $\pm$ s.d.	137.9 $\pm$ 0.5	96.2 $\pm$ 1.1	–	–99.5 $\pm$ 1.0	173.1 $\pm$ 0.5	104.2 $\pm$ 1.9

Table 4

Quantitative data obtained with H sample after the isothermal step at different temperature and time.

Isothermal $T$ and $t$	$T_{e,1^*}$ (°C)	$\Delta H_{1^*}$ (J g <sup>-1</sup> )	$T_{e,exo^*}$ (°C)	$\Delta H_{exo^*}$ (J g <sup>-1</sup> )	$T_{e,2^*}$ (°C)	$\Delta H_{2^*}$ (J g <sup>-1</sup> )
120 °C 12 h	137.2	96.1	143.4	–103.7	173.8	108.1
120 °C 24 h	137.3	93.5	142.5	–100.2	173.8	106.3
125 °C 12 h	135.2	76.7	140.4	–77.9	173.2	105.9
125 °C 24 h	137.2	64.6	141.1	–68.1	173.2	106.3
130 °C 12 h	136.8	14.1	140.3	–12.8	174.7	106.6
130 °C 24 h	–	–	–	–	173.4	106.6
Mean value $\pm$ s.d.	–	–	–	–	173.7 $\pm$ 0.6	106.6 $\pm$ 0.8

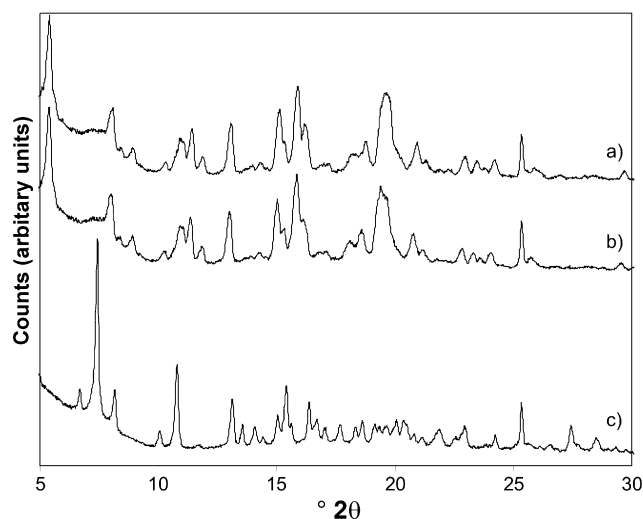


Fig. 6. X-ray patterns of H sample at different temperatures: room temperature (curve a), 120 °C (curve b) and 155 °C (curve c).

- the enthalpy change of the exothermic peak is the same (as absolute value), within the experimental error, as the one of the endothermic peak at 173 °C ( $\Delta H_{2^*}$ ).

3.2.2.2. *Cyclic measurements.* The goal of these measurements was to assess the reversible nature of the peaks. Cyclic measurements have been performed as follows:

- first heating at 2 K min<sup>-1</sup> up to 140 °C (temperature of the first endothermic peak closing) or up to 155 °C (temperature of the exothermic peak closing);
- cooling down to room temperature;
- second heating to 200 °C.

When the temperature reached in the first heating is 140 °C, during cooling an exothermic peak is recorded with a size corresponding to that of the exothermal peak present in a single run. On the contrary, when the temperature reached in the first heating is 155 °C, the cooling curve is flat. In the second heating, independently from the



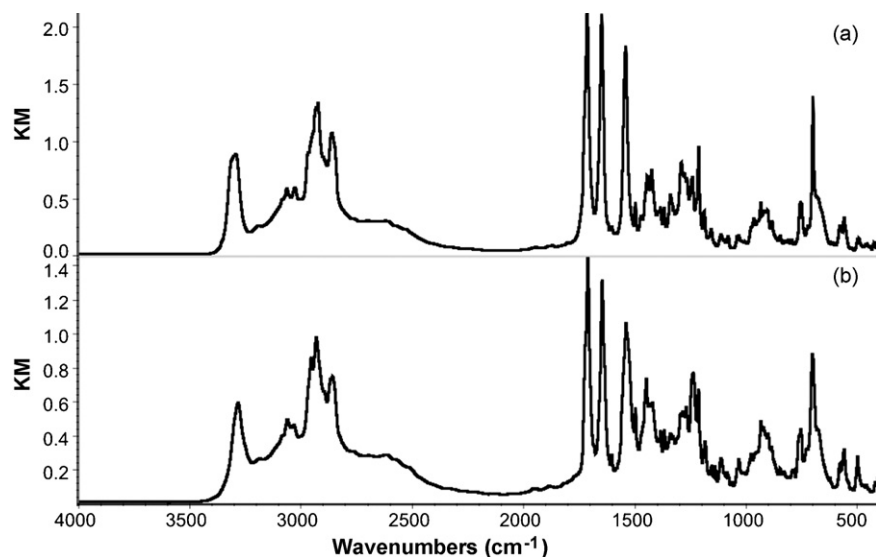


Fig. 7. FTIR spectra of H sample: original (curve a) and heated to 155 °C (curve b).

temperature reached in the first ramp, an endothermic peak, that can be superimposed to that present at 173 °C in a single run, is always recorded.

**3.2.2.3. Isothermal measurements.** Measurements with an isothermal step of 12 or 24 h have been carried out on H sample at different temperatures lower than melting temperature: 120 °C, 125 °C, 130 °C. As it can be seen in Table 4, the annealing at 120 °C does not modify the DSC trace of the sample but with increasing the

isothermal step temperature and time, the enthalpy changes of the peak at 137 °C ( $\Delta H_{1^+}$ ) and of the exothermic peak ( $\Delta H_{\text{exo}^+}$ ) become lower. These two effects disappear after 24 h at 130 °C. The enthalpy change of the peak at 172 °C ( $\Delta H_{2^+}$ ) is constant at  $106.6 \pm 0.8 \text{ J g}^{-1}$  and is the same as that measured for the melting of S polymorph obtained from annealing of B form.

**3.2.2.4. Discussion of DSC measurements.** The thermal measurements performed on the H sample can be interpreted with a model

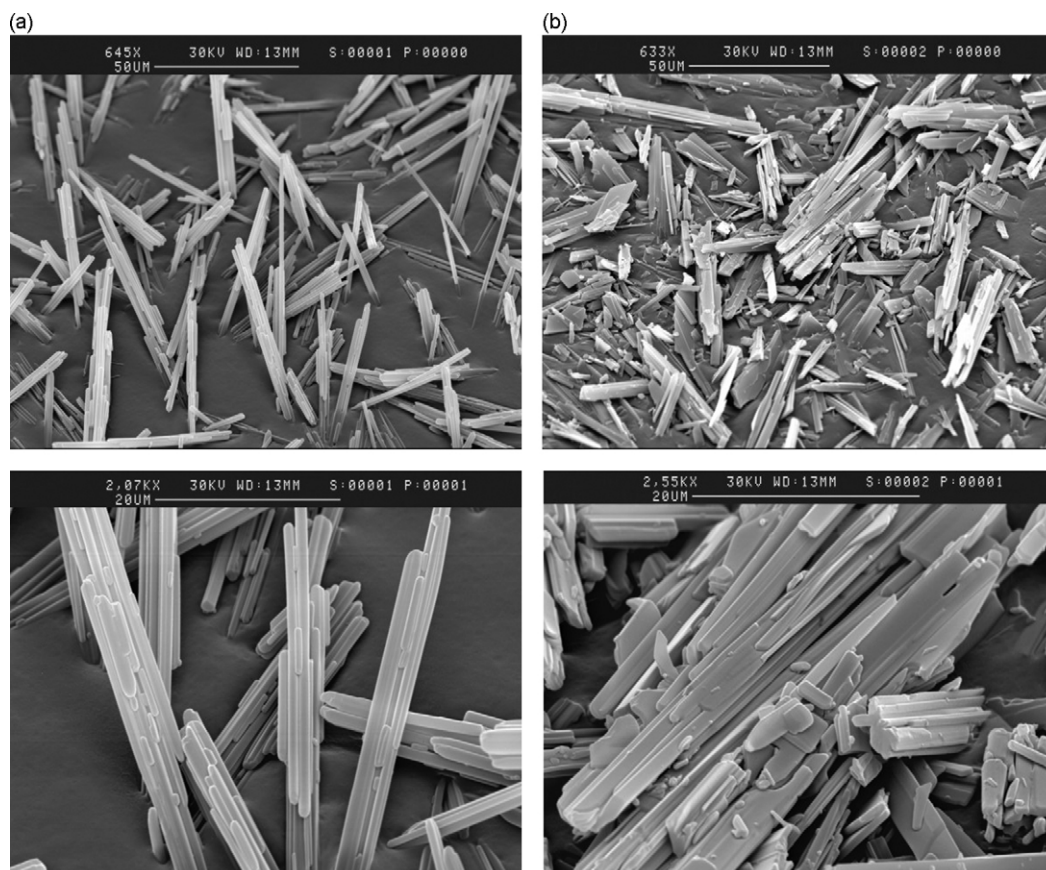


Fig. 8. SEM micrographs of H sample: original (column a) and conditioned 24 h at 130 °C (column b).

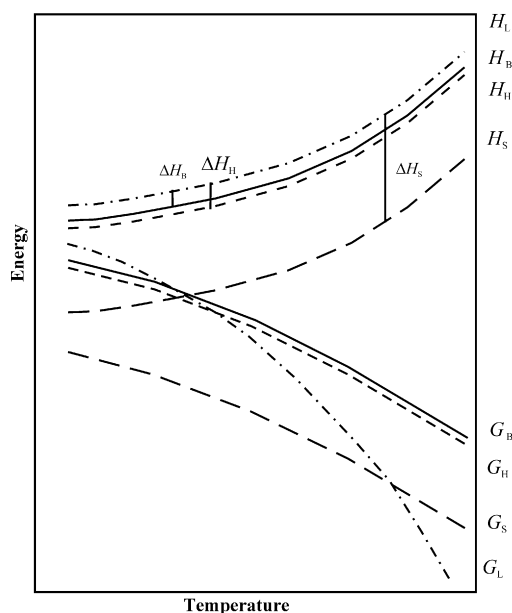


Fig. 9. Energy vs. temperature diagram of nateglinide polymorphs.

similar to that proposed for the B sample: with relatively low  $\beta$ , at 138 °C the melting of H form takes place followed by the crystallization of a new polymorph which in its turn melts at 173 °C. For the same reasons previously explained, we believe that also in this case it has to do with the polymorph named S in literature [2]. When the heating rate is relatively high, for kinetics reasons the crystallization from the melt is not possible: this is the reason why, with  $\beta \geq 10 \text{ K min}^{-1}$ , other thermal events, in addition to the one at 138 °C, are missing.

From DSC measurements with isothermal step before the sample melting we can infer that the annealing of H polymorph at temperature of at least 125 °C causes the polymorphic transition in solid phase to S form. In this case, the enthalpy change measured in a single run overlaps, within the experimental error, with that measured during the heating following the isothermal annealing. Therefore, we believe that original H sample does not contain amorphous portions.

### 3.2.3. X-ray measurements

X-ray analysis (Fig. 6) strongly supports the validity of the suggested model. As expected, after heating H sample at  $2 \text{ K min}^{-1}$  up to 120 °C (temperature lower than the sample melting) the pattern (curve b) is still the same as that of room temperature (curve a). At 155 °C (temperature corresponding to the exothermic peak), on the contrary, the trace (curve c) is definitely changed confirming the presence of a new crystalline form.

### 3.2.4. FTIR measurements

The FTIR measurements show that the spectra of H sample heated at  $2 \text{ K min}^{-1}$  up to 155 °C (temperature corresponding to the closing of exothermic peak) is the same as that of the H form annealed 24 h at 130 °C. Fig. 7 shows the spectra of the original sample (trace a) and of the sample heated up to 155 °C (trace b).

The spectrum of H form is sensibly different from that of the B form (see Fig. 3, trace a). On the contrary the spectra of H form and that of the sample heated up to 155 °C are sensibly closer to each other than it is the case with the B form (Fig. 3).

However some differences are present:

Table 5

Quantitative data of melting of nateglinide polymorphs.

Polymorph	$T_e$ (°C)	$\Delta H$ (J g <sup>-1</sup> )
B	129.2 ± 0.6	89.6 ± 2.4
H	137.9 ± 0.5	96.2 ± 1.1
S	174.1 ± 0.8	106.1 ± 2.0

- (i) amide III band (combination of C–N stretching and of the NH deformation) is at  $1290 \text{ cm}^{-1}$  in the H sample while it is at  $1238 \text{ cm}^{-1}$  in the heated sample;
- (ii) the in plane deformation of OH group coupled with C–O stretching is at  $1424 \text{ cm}^{-1}$  in the H sample while it is located at  $1238 \text{ cm}^{-1}$  in the heated sample.

The FTIR spectra suggest that a slightly different molecular structure is formed by heating the form H for 24 h at 130 °C.

### 3.2.5. SEM measurements

The morphology of original H sample and of sample H annealed 24 h at 130 °C is evident in Fig. 8. The original H polymorph is made of cylindrical sticks with some tens of  $\mu\text{m}$  in length and aligned to form blocks. After isothermal conditioning at 130 °C, the sticks maintain similar size but acquire squared contour and look like rectangular based parallelepipeds.

## 4. Conclusions

The information obtained from measurements performed on H and B samples has allowed to construct the energy vs. temperature diagram (Fig. 9) and to define the relationships of relative stability among the nateglinide polymorphs. The melting temperature ( $T_e$ ) and enthalpy changes ( $\Delta H$ ) values of the nateglinide polymorphs are summarized in Table 5 and we can conclude that they are all in relationship of monotropy [6]. The S form, the highest-melting form, is the only stable, while the polymorphs B and H are metastable forms.

The S polymorph can crystallize from the melt obtained from both B and H samples or also by an isothermal treatment of each form at a temperature lower than that of their melting: 24 h at 116 °C starting from B polymorph; 24 h at 130 °C starting from H polymorph.

All the three polymorphs show different crystal structure and, finally, the molecular structure is sensibly different as concerns forms B and H and B and S while it is much more similar between forms H and S.

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