THERMAL BEHAVIOUR OF MELT CRYSTALLIZED PHENYLBUTAZONE

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In the DSC curves, the melting point of phenylbutazone Form A was affected by the heating rate (first heat cycle). The DSC curves of the melt crystallized phenylbutazone (second heat cycle) showed the endothermic peaks of both Form C and Form A. The change in the first heat cycle of either the heating rate, the upper temperature limit, or the isothermal hold period at the upper temperature limit affected the value of the area ratio between the endothermic peaks of the two polymorphs in the DSC curves of the melt crystallized phenylbutazone. It was therefore suggested that the value of the area ratio is related to the energy supplied to the melt phenylbutazone in the first heat cycle. According to this hypothesis, the energy level that the melt should reach to crystallize as the metastable Form C should be higher than the essential one to crystallize as the stable Form A.

According to literature data, a lot of drugs exhibit polymorphic phenomena [1, 2], which can affect the drug bioavailability, stability, and solubility [3, 4].

Several methods allow to obtain the metastable forms of monotropic polymorphs [3, 4]. One of these methods is based on the melting of the drug, followed by a cooling procedure (melt crystallized product).

According to literature data [5-8], phenylbutazone can crystallize in several polymorphic forms. Different authors used different nomenclature for their polymorphs. However, from the evidence available it appears that Müller's Form δ [7] is equivalent both to Form IV of Ibrahim *et al.* [6] and to Form A of Tuladhar *et al.* [8], and that Müller's Form β [7] is equivalent to Form C of Tuladhar *et al.* [8].

The effect of the heating rate on the DSC melting point of the phenyl-
butazone polymorphic forms was shown for Müller's Form β [7] and for the
five forms (A-E) isolated by Tuladhar et al. [8].

Some authors [6, 7] also studied the melt crystallized phenylbutazone.
According to Müller [7], Form β can be prepared "by melting and recrystal-
lization of the commercial products, which were always available as form δ".
According to Ibrahim et al. [6] "Form IV, when heated up to 120°, cooled
either naturally or with liquid nitrogen, and then subjected to thermal
analysis, showed an endothermic peak at 97-98° instead of the original melt-
ing peak at 105°. On the other hand, slow controlled cooling of the melt
resulted in the regeneration of the original crystals, i.e., Form IV".

Therefore, this work aims to clarify the DSC behaviour of phenyl-
butazone crystallized from the melt by a cooling procedure (melt crystal-
lized phenylbutazone).

Experimental details

Materials

Phenylbutazone (4-butyl-1,2-diphenyl-3,5-pyrazolidinedione) was used as
received from the manufacturer (Aldrich). The X-ray diffraction pattern
agreed with those reported both for Form δ [7] and Form IV [6]. As both the
above forms are equivalent to Form A [8], the nomenclature proposed by
Tuladhar et al. [8] was used in this work. Form A was checked by thin-layer
chromatography [9]: no degradation products were shown.

Procedure

The DSC curves were recorded on a DSC-4 differential scanning
calorimeter equipped with a computerized data station (Perkin-Elmer). All
the samples (2.8-3.2 mg) were heated in crimped aluminium pans (Perkin-
Elmer) using dry nitrogen as the effluent gas (30 ml min^{-1}). Indium (99.99%,
Perkin-Elmer) (m.p. 156.60; ΔH 28.45 J/g) was used to check instrument
calibration. The determinations of the transition temperature and area were
made by a computerized procedure (Perkin-Elmer). Each melting point was
assumed to be the intersection point between the base line and the linear
section of the ascending endothermic curve, i.e., the onset.

The DSC analysis of the Form A of phenylbutazone (first heat cycle) was
carried out at different heating rates (2 deg/min, 10 deg/min, or 40 deg/min)

from the lower temperature limit of 30° to different upper temperature limits (110°, 120°, or 130°). As the upper temperature limit was reached, the melt product was immediately cooled to 30° (cooling rate 320 deg/min). When the melt product was obtained by the heating of Form A samples at a heating rate of 10 deg/min, in some cases it was also held for fixed time intervals (5 min, 10 min, or 30 min) (isothermal hold period) at one of the three upper temperature limits before the cooling procedure.

The melt crystallized phenylbutazone was always heated at the heating rate of 10 deg/min, 5 min after the cooling procedure (second heat cycle).

Results and discussion

1. First heat cycle (melting of Form A)

The DSC curves showed the influence of the heating rate on the melting point of Form A. As shown in Table 1, the melting point decreased as the heating rate decreased. Similar findings were already reported by Tuladhar et al. [8].

Table 1 The effect of the heating rate on the DSC melting point of phenylbutazone Form A. Standard deviation in parentheses.

Heating rate, deg/min	Melting point, °C
2	102.7(0.3)
10	103.6(0.2)
40	105.9(0.1)

2. Second heat cycle (melting of the melt crystallized phenylbutazone)

None of the DSC curves of the melt crystallized phenylbutazone (second heat cycle) showed only one transition peak, regardless of the experimental settings of the first heat cycle.

In all the DSC curves, the endothermic peak of the Form C melting (about 93°) was followed by one exothermic peak (96-97°) and by the endothermic peak of the melting of Form A (about 103°). The exothermic peak was the evidence of the crystallization process of Form A crystals in the melt of Form C, as pointed out for other polymorphs [10, 11]. The endothermic peaks were the evidence of the presence of both forms in the melt crystallized phenylbutazone. Form A and Form C could be present in the melt crys-

tallized phenylbutazone owing to their crystallization during the cooling procedure of the first heat cycle. On the other hand, Form A could be formed by a solid-state conversion of Form C into Form A during the heating procedure of the second heat cycle. This last hypothesis is unlikely, because the values of the area ratio between the peaks of Form C and Form A were not the same for all the melt crystallized samples. As the experimental conditions of the second heat cycle were the same for all the melt crystallized phenylbutazone samples, the value of the area ratio had to be constant. In fact, each process of polymorphic conversion has to be reproducible under the same experimental conditions. Even if no influence of the experimental conditions of the second heat cycle on the value of the peak ratio was possible, a partial conversion of Form C into Form A owing to the heating procedure cannot be quite excluded.

The experimental conditions of the first heat cycle (heating rate, upper temperature limit, and isothermal hold period) were the only differences in the preparation procedure of the different melt crystallized phenylbutazone samples. Therefore, their effect on the second heat cycle was analyzed.

Table 2 The effect of the heating rate and the upper temperature limit of the first heat cycle on the value of the area ratio between Form C (FC) and Form A (FA) peaks in the DSC curves of the melt crystallized phenylbutazone (second heat cycle). Heating rate of the second heat cycle 10 deg/min. Standard deviation in parentheses

Heating rate, deg/min	Upper temperature limit, °C	Area ratio FC/FA
2	110	1.6(0.2)
2	120	3.7(0.6)
2	130	10.2(0.9)
10	110	0.8(0.1)
10	120	2.1(0.2)
10	130	5.8(0.4)
40	110	0.6(0.1)
40	120	1.5(0.1)
40	130	4.2(0.4)

3. Effect of the experimental conditions of the first heat cycle on the second heat cycle

(a) Heating rate

The value of the area ratio between the peaks of Form C and Form A in the thermal curves of the second heat cycle increased as the heating rate of

the first heat cycle decreased (Table 2). Hence, the heating rate did not only affect the melting point of Form A, but also the respective amounts of both the polymers in the melt crystallized phenylbutazone.

Changes in the heating rate of the first heat cycle meant a different heating time of the melt phenylbutazone before the cooling procedure. Obviously, the heating time increased as the heating rate decreased. Furthermore, the heating time of the melt phenylbutazone changed also owing to the relationship between the melting point of Form A and the heating rate. In fact, it must be remembered that the melting point of Form A decreased as the heating rate decreased (Table 1).

(b) Upper temperature limit

Table 3 The effect of the upper temperature limit and of the isothermal   hold period at the upper temperature limit in the first heat cycle on the value of the area ratio between Form C (FC) and Form A (FA) peaks in the DSC curves of the melt crystallized phenylbutazone (second heat cycle). Heating rate of the first and second heat cycle 10 deg/min. Standard deviation ini parentheses

Upper temperature limit, °C	Isothermal hold period, min	Area ratio FC/FA
110	0	0.8(0.1)
110	5	3.9(0.6)
110	10	4.9(0.5)
110	30	9.2(0.2)
120	0	2.1(0.2)
120	5	5.3(0.3)
120	10	8.0(0.3)
120	30	12.1(1.4)
130	0	5.8(0.4)
130	5	10.2(0.8)
130	10	10.3(0.3)
130	30	11.8(1.1)

Changes in the upper temperature limit of the first heat cycle modified the value of the area ratio between the endothermic peaks in the curves of the second heat cycle. The ratio value increased as the upper temperature limit increased, regardless of the heating rate in the first heat cycle (Table 2).
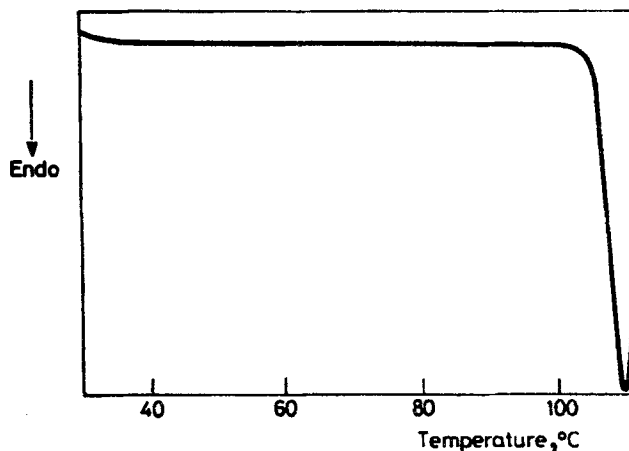
Fig. 1 DSC curve of phenylbutazone Form A (first heat cycle). Heating rate: 40 deg/min. Upper temperature limit: 110°C

When the first heat cycle was carried out at a heating rate of 40 deg/min up to the upper temperature limit of 110°, the endothermic peak of Form A melting stopped soon after having reached the peak maximum (Fig. 1). According to Tuladhar et al. [8] this behaviour should indicate only the melting of about half of the sample. Clearly, the incomplete melting affected the value of the area ratio in the second heat cycle.

However, these findings allow the conclusion to be drawn that the upper temperature limit of the first heat cycle affected the DSC curves of the second heat cycle.

(c) Isothermal hold period

The upper temperature limit of the first heat cycle being equal, the value of the area ratio between Form C and Form A peaks was differently affected by the isothermal hold period (Table 3). When the upper temperature limit was either 110° or 120°, the value of the area ratio increased as the isothermal hold period increased. On the contrary, when the upper temperature limit was 130°, the increase of the isothermal hold period from 5 min to 30 min did not affect the value of the area ratio.

The isothermal hold period of the first heat cycle being equal, the value of the area ratio in the thermal curves of the second heat cycle increased as the upper temperature limit of the first heat cycle increased.
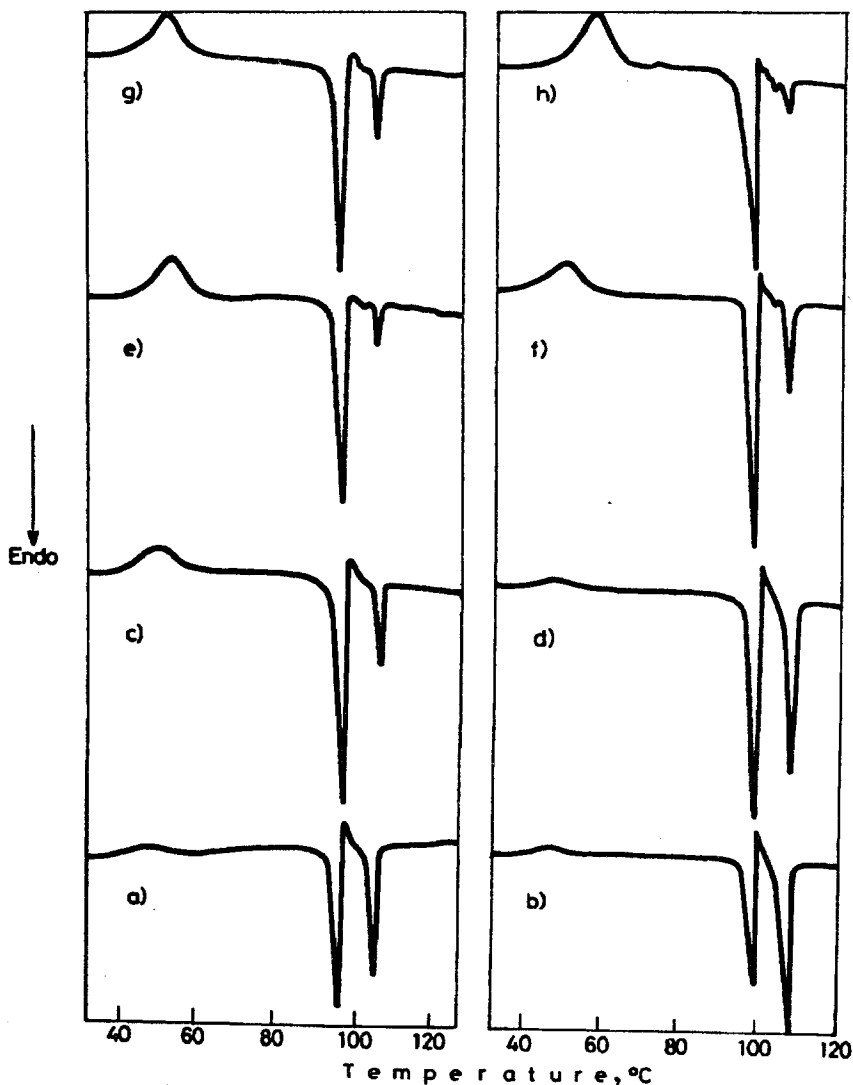
Fig. 2 DSC curves of the melt crystallized phenylbutazone (second heat cycle). Heating rate of the second cycle: 10 deg/min. Experimental conditions of the first cycle: A-Heating rate: 2 deg/min; upper temperature limit :110°C. B- Heating rate: 40 deg/min; upper temperature limit: 110°C. C-Heating rate: 2 deg/min; upper temperature limit : 120°C. D-Heating rate: 40 deg/min; upper temperature limit: 120°C. E-Heating rate: 2 deg/min; upper temperature limit: 130°C. F-Heating rate: 40 deg/min; upper temperature limit: 130°C . G-Heating rate: 10 deg/min; upper temperature limit: 120°C; isothermal hold period; 5 min. H-Heating rate: 10 deg/min; upper temperature limit:

4. Other thermal accidents in the thermal curves of the second heat cycle

A broad exothermic transition peak at about 40-50° was shown in all the DSC curves of the second heat cycle (Fig. 2). The area of this peak increased as in the first heat cycle either the heating rate decreased, the upper temperature limit or the isothermal hold period increased. The broad exothermic transition peak was the evidence of the crystallization process of a glassy amorphous product. As the increase of the area ratio between the peaks of Form C and Form A was affected by the experimental settings of
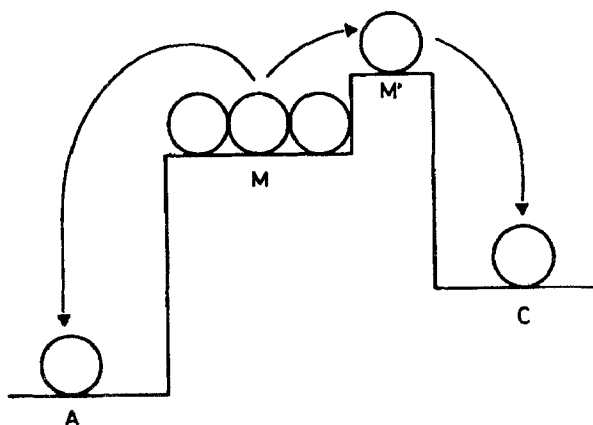

Fig. 3 Elementary mechanical model of the crystallization behaviour during the cooling procedure of the melt phenylbutazone

the first heat cycle, it is reasonable to suggest a correlation between the formation of Form C and that of the amorphous product. According to our working hypothesis, the amorphous product should crystallize into Form C during the second heat cycle.

Then, a third endothermic peak at an intermediate temperature (about 100°) between those of the melting of Form C and Form A appeared in some DSC curves of the second heat cycle (Fig. 2). The endothermic peak was never shown in these thermal curves when the first heat cycle was carried out at anyone of the three heating rates up to the upper temperature limit of 110° (Fig. 2A and B). Only when the upper temperature limit and the heating rate of the first heat cycle were 120° and 2 deg/min, respectively, the endothermic peak appeared in the thermal curves of the second heat cycle (Fig. 2C and D). Finally, the peak always appeared in the DSC curves of the melt crystallized samples, when the first heat cycle was carried out at any

one of the three heating rates up to the upper temperature limit of 130°
(Fig. 2E and F). In this case, the area of the peak increased as the heating
rate of the first heat cycle decreased. Furthermore, when the isothermal
hold period ranged from 5 min to 30 min, this peak was shown in the ther-
mal curves of the second heat cycle, regardless of the upper temperature
limit in the first heat cycle (Fig. 2G and H).

Thin-layer chromathography did not exhibit degradation products in the
samples showing this endothermic peak in the DSC curves of the second
heat cycle. Therefore, the endothermic peak should indicate the melting of a
polymorphic form different from Form A and Form C.

Conclusion

These findings are the evidence of a relationship between the experimen-
tal conditions of the melting process of Form A (first heat cycle) and the
thermal behaviour of the melt crystallized phenylbutazone (second heat
cycle).

The change of either the heating rate, or the upper temperature limit, or
the isothermal hold period allows to supply a different amount of heat to the
melt phenylbutazone. As the relationship between the heat and the energy
is obvious, the different experimental settings allow to supply different
amounts of energy to the melt phenylbutazone.

Our working hypothesis is visually described by the elementary mechani-
cal model shown in Fig. 3.

The spheres on the M plain have a stated kinetic energy and could drop
to either the A plain or the C plain. In the latter case, however, the spheres
have to reach the M' plain, which is higher than the M plain. Therefore the
spheres will more probably drop into the A plain. Should the kinetic energy
of the spheres increase, the number of the spheres reaching the higher M'
plain and dropping to the C plain, increases. A similar consideration can be
applied to the bahaviour of the melt phenylbutazone.

According to the heat supplied, the phenylbutazone molecules could
reach in the melt state a different mean energy level. The energy level where
the melt should need to crystallize as the metastable Form C should be
higher than the essential one to crystallize as the stable Form A. Therefore,
only the phenylbutazone molecules reaching a sufficient energy level in the
melt state could crystallize as the metastable Form C. Accordingly, the

amount of Form C in the melt crystallized phenylbutazone increases as the energy supplied to the melt product increases.

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Zusammenfassung - Bei der Aufname der DSC-Kurven wird der Schmelzpunkt von Phenylbutazon   Form   A   durch   die   Aufheizgeschwindigkeit   beeinflusst   (erster Aufheizzyklus). Die DSC-Kurven des aus der Schmelze kristallisierten Phenylbutazon (zweiter Aufheizzyklus) zeigt beide endothermen Peaks der Form C und Form A.

Eine Veränderung der Aufheizgeschwindigkeit, der oberen Temperaturgrenze oder der isothermen Wartezeit auf der oberen Temperaturgrenze des ersten Aufheizzyklus beeinflussen das Verhältnis der Flächen der endothermen Peaks der beiden polymorhen Formen in der DSC Kurve des aus der Schmelze kristallisierten Phenylbutazons. Es wird angenommen, daß der Wert für das Verhältnis der Flächen eine Funktion der im ersten Aufheizzyklus für das geschmolzene Phenylbutazon aufgewendeten Energie ist. In Übereinstimmung mit dieser Hypothese müßte das Energieniveau, welches die Schmelze erreichen muß, um als metastabile Form C zu kristallisieren, höher liegen als jenes, bei der sie als stabile Form A kristallisiert.