

## Research Paper

# Evidence for a New Crystalline Phase of Racemic Ibuprofen

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**Purpose.** The aim of this work is to search for the existence of crystalline polymorphism for racemic Ibuprofen.

**Methods.** The pharmaceutical material was studied by X-ray diffraction to identify crystalline phases, and by Differential Scanning Calorimetry to follow the thermodynamic evolution of these forms *versus* temperature.

**Results.** Results presented here show that, in addition to the already known conventional crystalline phase, whose nucleation domain extends between 233 K and 263 K and which melts at 349 K, racemic Ibuprofen can crystallize in another polymorphic phase. The nucleation of this new polymorphic variety is triggered by a stay at least 60 degrees below the glass transition temperature  $T_g$  of Ibuprofen ( $T_g=228$  K). This nucleation is probably of heterogeneous type. The new phase melts well below the conventional one, i.e. at 290 K. A schematic free energy diagram is provided allowing establishing the relative thermodynamic stability of the two polymorphs.

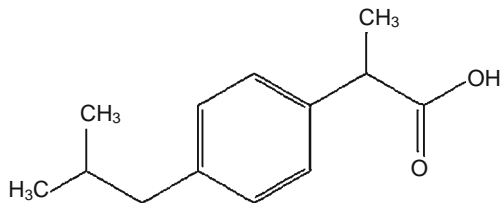
**Conclusions.** These results establish, for the first time, that Ibuprofen can exist under two different crystalline phases which constitute a monotropic system, the new form being metastable.

**KEY WORDS:** glass transition; ibuprofen; nucleation; polymorphism.

## INTRODUCTION

Crystalline pharmaceutical compounds are known to generally exist under several polymorphic forms. As defined by Bernstein (1), "polymorphism is the ability of a substance to exist in two or more crystalline forms that have a different arrangement and/or conformation of molecules in a crystalline lattice". The search for these polymorphic varieties recently became a topic of major interest since they have different physical properties (solubility, melting temperature,...) and can lead to instability that has dramatic consequences. The aim of this study is to search for the possible existence of a polymorphic crystalline form of the active pharmaceutical ingredient: Ibuprofen.

Ibuprofen, 2(4-isobutylphenyl)propanoic acid, of molecular weight  $M=206.29$  g/mol, is a widely used non-steroidal anti-inflammatory drug having analgesic and antipyretic activities. It is currently available as a racemic mixture of S(+)-Ibuprofen and R(-)-Ibuprofen; S(+)-Ibuprofen is the pharmacologically active form (2). Its molecular structure is as follow:



A lot of studies have shown that different crystals morphologies (habit, size, surface area) of racemic Ibuprofen can be obtained depending on the preparation and the used solvents (3–6). But, to our knowledge, these different forms are structurally isomorphic and there is no true crystalline polymorphism (as defined above). Up to now, the only known crystallographic form for racemic Ibuprofen has a monoclinic  $P21/c$  space group (7–8). In this study of racemic Ibuprofen, we will show for the first time that a new polymorphic crystalline variety can be identified which can be obtained by specific re-crystallization of the supercooled liquid Ibuprofen. Systematic Differential Scanning Calorimetry (DSC) investigations of the vitrification and crystallization of the compound will allow us to locate the preferred temperature zones of nucleation and growth for the two polymorphic varieties with regards to the glass transition temperature  $T_g$ . This study will also lead to establish the melting properties of the two polymorphs and to discuss their relative stability. Moreover, X-ray diffraction will be used to identify the structural signatures of the crystalline structures.

## MATERIALS AND METHODS

### Material

Racemic Ibuprofen was purchased from Sigma (CAS 15687-27-1), catalogue number I4883, lot number 026H1368. The purity is 99.8% (gas chromatography assay). Samples were analysed without further purification.

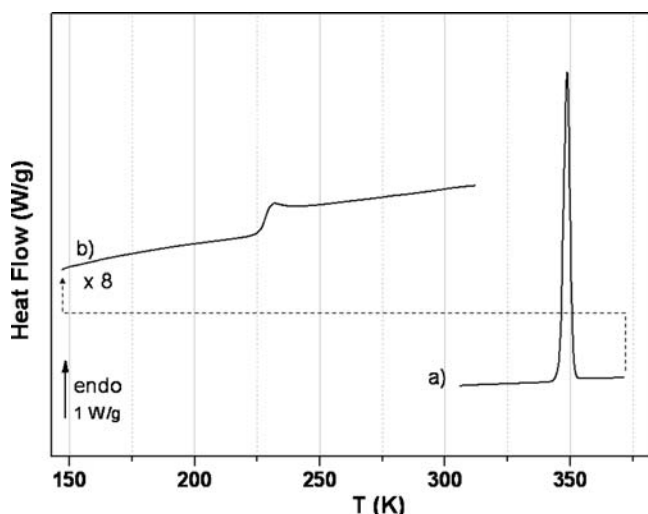
### Methods

The powder X-ray diffraction experiments were performed with an INEL CPS 120 diffractometer ( $\lambda_{CuK\alpha1}=1.54056$  Å) equipped with a 120° curved position sensitive

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**Fig. 1.** DSC thermograms recorded at 10 K/min of racemic Ibuprofen a) initially crystalline (conventional phase) and b) after a quench at 20 K/min from 373 K to 143 K.

detector coupled to a 4096 channel analyzer. A Cryostream Plus controller from Oxford Cryosystems was used to regulate the temperature. Samples were placed into Lindemann glass capillaries ( $\phi=0.7$  mm).

Differential Scanning Calorimetry (DSC) experiments were carried out in a DSC Q10 from TA Instruments with a heating rate of 10 K/min. A small amount of sample (less than 5 mg) was enclosed in a hermetic aluminum pan. Measurements were realized under dry helium (at flow rate of 25 ml/min) to improve the thermal conductivity. A liquid nitrogen cooling system was used in order to reach temperatures as low as 143 K. Temperatures and enthalpies were calibrated using Indium at the same heating rate and the same environmental conditions as the experiments.

## RESULTS

### Vitrification

At ambient temperature, Ibuprofen is a white crystal. Under heating (at 10 K/min), this crystalline form melts at 349 K, which gives rise to an endothermic peak on a DSC scan (cf. Fig. 1a). This melting temperature is typical of the racemic mixture (9–10). The melting enthalpy is  $25.8 \pm 0.5$  kJ/mol, in agreement with the value reported by Xu and co-workers (11).

When this melted Ibuprofen is quenched to 143 K (at 20 K/min for example), crystallization is avoided (absence of an exothermal peak on DSC thermogram) and, on subsequent heating at 10 K/min, a heat flow jump can clearly be seen between 223 K and 238 K which is the characteristic signature of the glass transition (cf. Fig. 1b). We found  $T_g = 228 \pm 1$  K (inflexion point temperature), in agreement with the value obtained by Brás and co-workers (12) and Johari and co-workers (13). The heat capacity jump at the glass transition is  $76 \pm 1$  J/mol.K. Ibuprofen can thus be amorphized by a quench from the melt and appears to be a good molecular glass former.

### Nucleation and Crystal Growth of the Conventional Phase

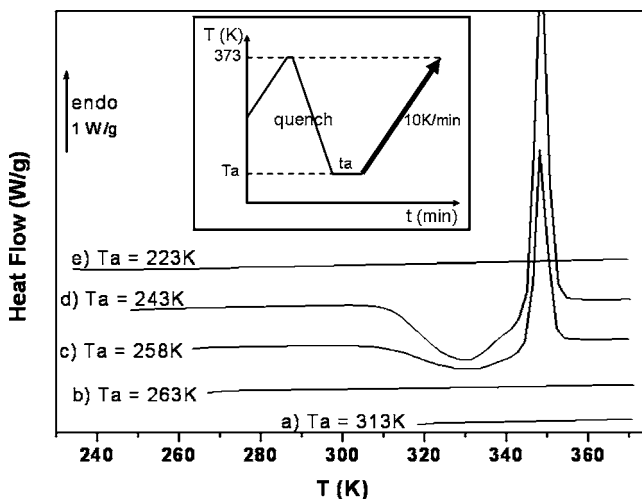
A series of DSC experiments have been made on supercooled liquid Ibuprofen in order to study the conditions for nucleation and crystal growth. The protocol presented in the inset of Fig. 2 is as follows. After melting (heating till 373 K), the Ibuprofen sample is quenched (at 20 K/min) till an annealing temperature  $T_a$  (ranging from 323 K to 213 K) where it is held for  $t_a$  ( $t_a=0$  min, 180 min or 360 min). Heat flow is then recorded as the sample is re-heated till 373 K (at 10 K/min). As an example, the scans recorded after annealing for 360 min at 313 K, 263 K, 258 K, 243 K and 223 K are reported on Fig. 2 (scans a to e).

Crystallization is never observed during the cooling but it appears that, depending on the annealing temperature, a recrystallization of the sample can be observed upon heating.

Indeed, when supercooled liquid Ibuprofen is annealed at a temperature superior or equal to 263 K, no recrystallization of the sample is observed on subsequent heating, even after a 360 min annealing (Fig. 2, scans a and b). After an annealing of the supercooled liquid between 263 K and 233 K, an exothermic peak characteristic of a crystallization process is observed—on heating—between 300 K and 343 K (Fig. 2, scans c and d). This peak is immediately followed by an endothermic peak at 349 K characteristic of the melting of the conventional crystalline phase. During the annealing, the sample has thus recrystallized towards the starting crystalline phase.

When the sample is quenched to an annealing temperature ranging from 233 K to 213 K (Fig. 2, scan e), results are more erratic but, statistically, the sample does not recrystallize upon heating.

These results can be interpreted in terms of a nucleation/growth process (14–15). According to these results, it appears that the nucleation temperature range of the conventional phase of Ibuprofen is between 233 K and 263 K. So, when the sample is not cooled below 263 K, there is no nucleation and, on subsequent heating, crystallization cannot occur. When the sample is cooled to a lower temperature range, between



**Fig. 2.** DSC thermograms (recorded at 10 K/min) of racemic Ibuprofen after a quench from the melt (at 20 K/min) to  $T_a$  and an annealing at  $T_a$  for  $t_a=360$  min (see inset). a)  $T_a=313$  K, b)  $T_a=263$  K, c)  $T_a=258$  K, d)  $T_a=243$  K, e)  $T_a=223$  K.

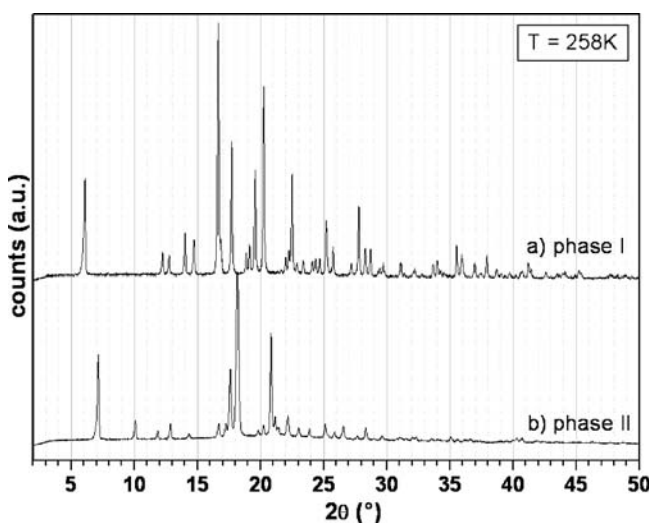
233 K and 263 K, the nuclei formation becomes thermodynamically favorable; on re-heating at 10 K/min, crystal growth occurs around 330 K and, consequently, the sample crystallizes. Nucleation rate ( $N$ ) and growth rate ( $G$ ) are expected to both have a maximum resulting from the competition between the thermodynamic driving force increase and the molecular motions slowing down. It stands out from Fig. 2 that the  $G$  maximum is located near 330 K. At this temperature, the observation of a larger exotherm after an annealing at 243 K allows locating the  $N$  maximum near this temperature. It thus appears from this study that both maxima are well separated in temperature, which explains the good glass forming ability of Ibuprofen. When the sample is quenched below 233 K, the molecular mobility becomes too slow for nuclei to form (fast increase of viscosity on approaching the glass transition). On subsequent heating at 10 K/min, the heating rate is too fast for nuclei to appear in the 233–263 K temperature range and finally no crystallization can be detected. However, if some nuclei could appear below 233 K, the sample would partly re-crystallize upon reheating, which explains erratic results.

### X-ray and Calorimetric Evidence of a New Polymorph

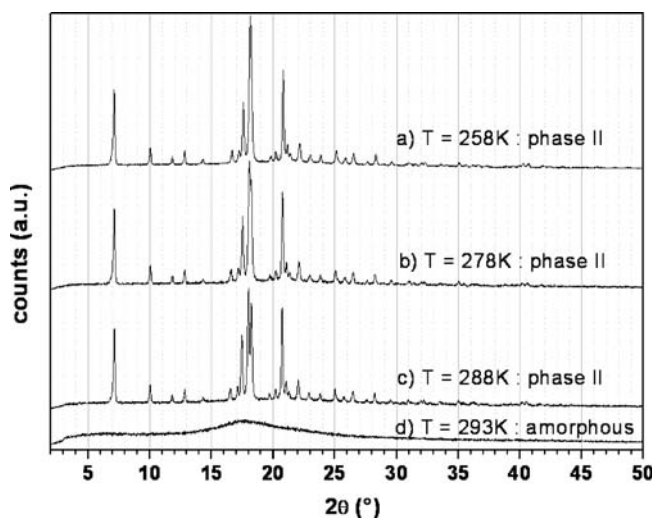
A specific thermodynamic treatment implying stays at very low temperatures and further annealing at appropriate temperatures, allows us to identify a new phase by X-ray diffraction and DSC experiments.

#### a) X-ray diffraction

The reference X-ray powder diffraction pattern of the conventional crystalline Ibuprofen recorded at 258 K is reported on Fig. 3a. Clear, intense and sharp Bragg peaks can be seen. Their positions are in agreement with the diffraction pattern of the racemic form whose structure has been determined as belonging to the monoclinic  $P21/c$  space group by McConnell (7) and Shankland *et al.* (8).



**Fig. 3.** X-ray diffraction pattern recorded at 258 K of racemic Ibuprofen a) initially crystalline (conventional phase) and b) after a cooling from the melt to 143 K where it is held for 1 hour, a heating to 258 K (at 6 K/min) and a 15 hours annealing at 258 K. Data are collected, for each case, for 900 s.

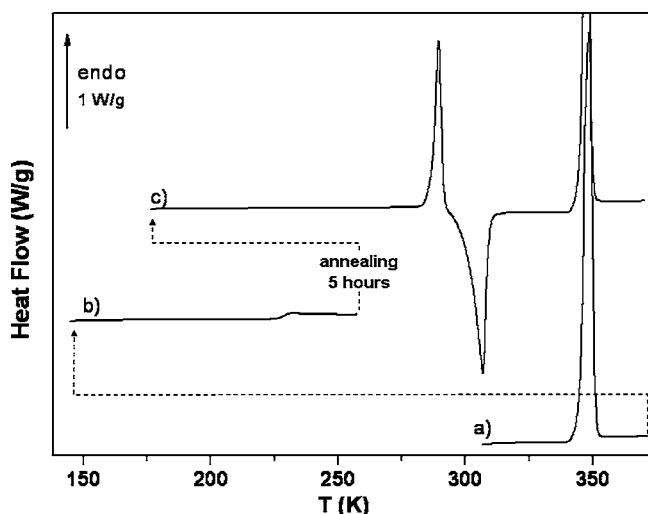


**Fig. 4.** X-ray diffraction pattern of racemic Ibuprofen initially in the form II recorded at a) 258 K, b) 278 K, c) 288 K, then d) 293 K. Data are collected, for each case, for 900 s.

The new polymorphic variety can be obtained by imposing the following thermal history to the sample. The crystalline powder, enclosed in the X-ray capillary, is melted (heating to 373 K), then cooled at 6 K/min till 143 K where it is annealed for 1 hour. The sample is then heated to 258 K (with a heating rate of 6 K/min) and held at this temperature for  $t_a=15$  hours. A X-ray diffraction pattern is recorded every hour. On the first recording, a halo characteristic of an amorphous phase is observed on the obtained pattern and no Bragg peak can be seen: after the cooling to 143 K and the heating to 258 K, the Ibuprofen sample is still amorphous. After one hour at 258 K, some Bragg peaks appear and their magnitude increases upon further annealing: the sample slowly crystallizes. After 5 hours, intense and thin peaks can be seen and no evolution is noted for the 10 following hours. The diffraction pattern obtained after the 15 hours annealing is reported on the Fig. 3b.

The comparison of the diffraction patterns of the initial crystal state and of the amorphous sample re-crystallized at 258 K (Fig. 3a and b) clearly indicates that the two crystalline phases are different. It should be noted that the diffraction pattern does not correspond either to the S(+)-Ibuprofen (16). As a consequence of the specific treatment, a new crystalline form of Ibuprofen has thus appeared at 258 K. It can be observed that, at wide angles, the peaks of the new form are clearly less intense than those of the conventional form. This leads us to suspect that the new crystalline form is more disordered. However, since the Bragg peaks are sharp, such a disorder should be compatible with a great crystallographic perfection, as it is the case for example for crystals with huge thermal agitation or for rotator crystalline phases (so-called plastic crystals) (17). In the following, for sake of clarity, the conventional crystalline phase will be called “phase I” and the new crystalline form, “phase II”.

Diffraction X-ray patterns of the sample crystallized upon phase II are then recorded every 5 degrees as the temperature increases. Till 288 K (Fig. 4a, b and c), no major evolution is observed on the diffraction pattern. With increasing temperature, only occur the usual peak shifts to lower Bragg angles, which indicate volume expansion. The



**Fig. 5.** DSC thermograms recorded at 10 K/min of racemic Ibuprofen a) initially in the form I, b) after a quench from 373 K (at 20 K/min) to 143 K where it is held 1 hour, c) after a 5 hours annealing at 258 K and a quench to 173 K.

split of the peak occurring near  $18^\circ$  has to be attributed to different expansion coefficients in the different crystallographic directions. On the pattern recorded at 293 K (pattern 4d), Bragg peaks have completely disappeared and only a halo characteristic of an amorphous phase can be seen. This means that the crystalline phase II has melted and the sample is amorphous. The melting temperature of this new crystalline form is thus located between 288 K and 293 K, well below the melting temperature of the crystalline phase I.

#### b) DSC experiments

In order to gain information on melting properties and physical stability of phase II, a systematic DSC study has been realized. A thermal treatment similar to the previous X-ray experiment is used. The Ibuprofen sample (encapsulated in a hermetic pan) is melted (heated to 373 K at 10 K/min) (scan a of Fig. 5), then quenched at 20 K/min to 143 K, where it is held for one hour. Then, the sample is heated to 258 K at 10 K/min (scan b of Fig. 5) and annealed for 5 hours at this temperature. To observe the effect of this thermal treatment, the sample is finally quenched to 173 K at 20 K/min and a thermogram is recorded upon subsequent heating at 10 K/min till 373 K (scan c of Fig. 5).

On the scan 5a, the melting of the crystalline phase I appears at 349 K as previously reported. The quench to 143 K prevents the sample from re-crystallizing and, on the scan 5b, the heat flow jump characteristic of the glass transition can clearly be seen at 228 K. On the scan 5c (after the 5 hours annealing at 258 K), no heat flow jump can be seen anymore around 228 K: the sample has crystallized during the annealing. Moreover, an endothermic peak is observed at 290 K. This temperature corresponds to the temperature range where the Bragg peaks characteristic of the phase II disappeared in the X-ray experiment. This endothermic peak is thus due to the melting of the crystalline phase II of Ibuprofen which has crystallized during the annealing at 258 K. It should be noted that, since in the X-ray experiments the Bragg peaks are thin, this low temperature melting cannot be associated with the melting of very small crystals of phase I

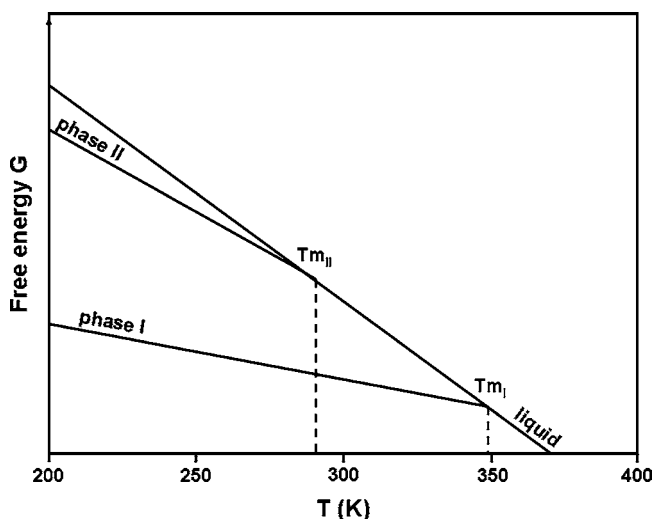
via a Gibbs-Thomson effect. Neither can this endothermic event be associated with a solid–solid transition as the X-ray pattern recorded at 293 K is characteristic of an amorphous phase. From the DSC data we obtained a melting enthalpy for this new crystalline phase of  $7.0 \pm 0.5$  kJ/mol.

It has to be pointed out that, after the melting of the phase II, a re-crystallization of the sample can be observed around 310 K (followed by the corresponding melting at 349 K) as illustrated in Fig. 5c. However, this is not a systematic behavior and the sample otherwise remains in its amorphous liquid form.

## DISCUSSION

### Gibbs Free Energy Diagram

The results presented here reveal that Ibuprofen can exist under two different crystalline phases: the conventional phase I, which melts at 349 K, and a new phase II that melts at 290 K. Two different types of Gibbs energy diagram can be considered: phases I and II form either a monotropic or an enantiotropic system. In the monotropic case, one of the forms would be stable in the entire domain of existence (phase I) and the other one would always be metastable (phase II). In the enantiotropic case, each crystalline form would have its domain of stability. In this latter case, an endothermic solid to solid phase transition can be expected if the recording rate is low enough. But we could not find evidence of such a calorimetric signature. According to the heat-of-fusion rule proposed by Burger and Ramberger (18–19), the form with the higher melting point presents the smaller melting enthalpy if the system is enantiotropic. On the contrary, if the form with the higher melting point also presents the higher melting enthalpy, the system is expected to be monotropic. The applicability of this criterion may be difficult when the lower temperature endotherm is immediately followed by a re-crystallization exotherm. The latter may contribute to artificially lower the true value of the melting enthalpy of the metastable phase. Our results indicate



**Fig. 6.** Semi-schematic Gibbs free energy diagram of racemic Ibuprofen.



that the melting enthalpy of the phase I (fusion at 349 K) is  $25.8 \pm 0.5$  kJ/mol, and that the one of the phase II (fusion at 290 K) is  $7.0 \pm 0.5$  kJ/mol. We may notice that the exotherm at 306 K is rather well separated from the endothermic peak. This leads us to admit that the value of the enthalpy associated to this latter peak is not very much affected by the occurrence of this exotherm. The latter corresponds to the crystallization of phase I from the melted phase II. The relative value of the two melting endotherms seems to establish that the two crystalline phases of Ibuprofen form a monotropic set. Phase II is thus metastable. Work is in progress to verify this suggestion. From the value of the melting enthalpies and temperatures, it is possible to calculate the melting entropies, which are respectively  $74 \pm 2$  J/mol.K and  $24 \pm 2$  J/mol.K for phase I and II. The entropy values allow us to compare the slope of the Gibbs free energy *versus* temperature curves and to propose the semi-schematic Gibbs diagram of racemic Ibuprofen shown in Fig. 6. The small gap which is observed between the liquid and the phase II energies seems to corroborate the X-ray observations that phase II may be disordered.

### Nucleation Below $T_g$

The conditions of formation of the two polymorphic phases have revealed very specific conditions for the nucleation processes of the two phases.

On the one hand, experiments on phase I of Ibuprofen have shown that the nucleation process of this phase preferentially develops between 233 K and 263 K. Upon further heating, the nuclei are observed to grow with a maximum rate around 330 K. The DSC heating scan of Fig. 2c shows such a re-crystallization of the sample toward phase I, after a direct quench from the melt at 258 K and annealing at this temperature which induces nucleation of phase I.

On the other hand, the results presented on Fig. 5c show that, this time, during the annealing at 258 K of the liquid initially quenched to a much lower temperature ( $T_a = 143$  K), a re-crystallization of the melt toward phase II occurs. In fact, we have observed through complementary experiments that the appearance of form II of Ibuprofen at 258 K is linked to a stay of the quenched liquid at very low temperatures, i.e. at least lower than  $T_g - 60$  K, even for a short time. This means that the nucleation of phase II is triggered by an excursion of the sample down to temperatures situated at least 60 degrees below the glass transition. This result is quite intriguing because of the very low temperature range it is located in, but such a phenomenon has already been observed by Oguni and co-workers for other materials as salol (20) or o-benzylphenol (21), and Legrand and co-workers on meta-toluidine (22). It should be noted that, during the quench of the liquid, erratic thermodynamic events appeared on the DSC scans at temperatures lower than approximately 170 K. These artifacts are due to physical jumps of the pan encapsulating the sample in the DSC oven. These jumps are provoked by a sudden release of energy (peak of heat flow on the thermogram) which is most probably due to sudden cracks formation in the glassy sample. Similar behavior was observed for meta-toluidine (22). In this latter case, it has been shown that nucleation occurs below  $T_g$  but it is assisted by formation of

cracks, which are observed to systematically occur at about  $T_g - 35$  K. These cracks are the support of heterogeneous nucleation, which amplifies nucleation rate. However, upon heating, cracks are cured just below  $T_g$ . Consequently the cracks assisted nucleation process must occur in a temperature range where the time scale of the molecular motion is considerably lowered. This leads us to suspect a decrease of the nucleation barrier at very low temperature, which is not predicted by the classical Becker-Döring theory (23).

### CONCLUSION

This DSC and X-ray study of racemic Ibuprofen has revealed a solid state polymorphism for this compound. In addition to the well-known crystalline phase I, which melts at 349 K, we were able to observe, for the first time, the development of another crystalline phase II which melts at a lower temperature, 290 K, and is thus of lower stability. The appearance of this form is conditioned by a quench of the liquid till very low temperatures, at least 60 degrees below  $T_g$ . This emphasizes the possibility of the occurrence of a nucleation process far below  $T_g$  as already observed by Legrand *et al.* (22) and Oguni *et al.* (20–21) on other molecular compounds. The nuclei of phase II then grow around 260 K, which is also curiously the preferred nucleation zone of phase I. The possible kinetic interplay of the crystallization processes of the two phases explains the difficulty to establish polymorphism of Ibuprofen. The comparison of the melting enthalpies of the two forms and the absence of endothermic solid-to-solid transformation leads us to strongly suspect that these two polymorphic varieties form a monotropic set: the conventional phase I is the stable form and the phase II is metastable. The discovery of this metastable form of presumably much higher solubility may be interesting for drug formulation. However the stability of the phase II with regards to the one of the phase I is an important question to address. Work is in progress to characterize possible exothermic transformation from phase II to phase I and their kinetics.

### ACKNOWLEDGMENTS

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### REFERENCES

1. J. Bernstein. *Polymorphism in molecular crystals*, Oxford Science, Oxford, 2002. J. Bernstein. *Polymorphism in molecular crystals*. Oxford Science, Oxford, 2002.
2. S. S. Adams, P. Bresloff, and C. G. Manson. Pharmacological differences between the optical isomers of ibuprofen: evidence for metabolic inversion of ibuprofen. *J. Pharm. Pharmacol.* **28**:256–257 (1976).
3. N. Rasenack, and B. B. W. Müller. Properties of Ibuprofen crystallized under various conditions: a comparative study. *Drug. Dev. Ind. Pharm.* **28**:1077–1089 (2002). doi:10.1081/DDC-120014575.
4. N. Rasenack, and B. B. W. Müller. Crystal habit and tableting behavior. *Int. J. Pharm.* **244**:45–57 (2002). doi:10.1016/S0378-5173(02)00296-X.

5. A. H. Nada, S. M. Al-Saidan, and B. W. Mueller. Crystal modification for improving physical and chemical properties of ibuprofen. *Pharm. Technol.* **29**:90–101 (2005). (Nov).
6. T. Lee, C. S. Kuo, and Y. H. Chen. Solubility, polymorphism, crystallinity, and crystal habit of acetaminophen and ibuprofen. *Pharm. Technol.* **30**:72–92 (2006). (Oct.).
7. J. F. McConnell. 2-(4-Isobutylphenyl) propionic acid. C<sub>13</sub> H<sub>18</sub> O<sub>2</sub> ibuprofen or prufen. *Cryst. Struct. Comm.* **3**:73–75 (1974).
8. N. Shankland, C. C. Wilson, A. J. Florence, and P. J. Cox. Refinement of ibuprofen at 100 K by single-crystal pulsed neutron diffraction. *Acta Cryst.* **C53**:951–954 (1997). doi:10.1107/S0108270197003193.
9. S. Lerdkanchanaporn, and D. Dollimore. A thermal analysis study of ibuprofen. *J. Therm. Anal.* **49**:879–886 (1997). doi:10.1007/BF01996773.
10. A. J. Romero, L. Savastano, and C. T. Rhodes. Monitoring crystal modifications in systems containing ibuprofen. *Int. J. Pharm.* **99**:125–134 (1993). doi:10.1016/0378-5173(93)90354-I.
11. F. Xu, L. X. Sun, Z. C. Tan, J. G. Liang, and R. L. Li. Thermodynamic study of ibuprofen by adiabatic calorimetry and thermal analysis. *Thermochim. Acta.* **412**:33–37 (2004). doi:10.1016/j.tca.2003.08.021.
12. A. R. Brás, M. Dionisio, and N. T. Correia. Molecular motions in amorphous pharmaceuticals. In *Proceedings of IWCS 2007, AIP CP 982*:91–97 (2008).
13. G. P. Johari, S. Kim, and R. M. Shanker. Dielectric relaxation and crystallization of ultraviscous melt and glassy states of Aspirin, Ibuprofen, Progesterone, and Quinidine. *J. Pharm. Sci.* **96**:1159–1175 (2007). doi:10.1002/jps.20921.
14. K. F. Kelton. Crystal nucleation in liquids and glasses. In H. Ehrenreich, and D. Turnbull (eds.), *Solid State Physics*, Academic, San Diego, 1991, pp. 75–177.
15. J. E. Shelby. Introduction to glassy science and applications. Royal Society of Chemistry, Cambridge, United Kingdom, 2002.
16. N. V. Phadnis, and R. Suryanarayanan. Simultaneous quantification of an enantiomer and the racemic compound of ibuprofen by X-ray powder diffractometry. *Pharm. Res.* **14**:1176–1180 (1997). doi:10.1023/A:1012198605891.
17. A. Guinier. *X-ray crystallographic technology*, Hilgerand Watts, Hilger Division, London, 1952. A. Guinier. *X-ray crystallographic technology*. Hilgerand Watts, Hilger Division, London, 1952.
18. A. Burger, and R. Ramberger. On the polymorphism of pharmaceuticals and other molecular crystals. I. Theory of thermodynamic rules. *Mikrochimica Acta.* **II**:259–271 (1971).
19. A. Burger, and R. Ramberger. On the polymorphism of pharmaceuticals and other molecular crystals. I. Applicability of thermodynamic rules. *Mikrochimica Acta.* **II**:273–316 (1971).
20. F. Paladi, and M. Oguni. Generation and extinction of crystal nuclei in an extremely non-equilibrium glassy state of salol. *J. Phys. Condens. Mater. Surf. Interfaces Biophys.* **15**:3909–3917 (2003). doi:10.1088/0953-8984/15/23/306.
21. F. Paladi, and M. Oguni. Anomalous generation and extinction of crystal nuclei in nonequilibrium supercooled liquid o-benzylphenol. *Phys. Rev. B.* **65**:144202 (2002). doi:10.1103/PhysRevB.65.144202.
22. V. Legrand, M. Descamps, and C. Alba-Simionesco. Glass-forming meta-toluidine: a thermal and structural analysis of its crystalline polymorphism and devitrification. *Thermochim. Acta.* **307**:77–83 (1997). doi:10.1016/S0040-6031(97)00271-2.
23. R. Becker, and W. Döring. Kinetische Behandlung der Keimbildung in übersättigten Dämpfen. *Annalen der Physik.* **24**:719–752 (1935). doi:10.1002/andp.19354160806.