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Determination of the crystal structure of nifedipine form *C* by synchrotron powder diffraction

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The crystal structure of the metastable form *C* polymorph of nifedipine [$C_{17}H_{18}N_2O_6$, 3,5-dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate] was determined by means of direct-space techniques applied to high-resolution synchrotron powder diffraction data. The polymorph crystallizes in the space group $P\bar{1}$ and exhibits a molecular packing significantly different from that of the stable modification, with molecules aligned in an orthogonal configuration inside the unit cell. The molecular conformation, on the other hand, remains substantially unmodified between the two polymorphs. Additionally, *in situ* thermal characterization of nifedipine crystallization behaviour was performed, confirming the nucleation of another metastable polymorph (form *B*) prior to the complete crystallization of the stable modification. A complete structural characterization of form *B* was not possible owing to its very limited stability interval.

1. Introduction

Polymorphism, namely the occurrence of chemical compounds characterized by the same structural formula but different crystal forms, is a phenomenon of fundamental importance in organic chemistry from theoretical and practical aspects (Bernstein, 2002). Different molecular arrangements along the periodic lattice may cause considerable variations in the physical and chemical properties of the compound, such as thermal stability, solubility and colour. In particular, polymorphism in pharmaceutical solids may manifest itself with significant alteration of the bioavailability and toxicity characteristics (Brittain, 2009, 2010). In many cases metastable polymorphs may arise as a by-product of industrial fabrication processes (*e.g.* mechanical milling, hot-melt extrusion *etc.*), calling for an accurate screening of the commercial product (Chemburkar *et al.*, 2000). The importance of polymorph screening during drug design and synthesis has thus been steadily increasing in recent years. Single-crystal X-ray diffraction is the method of choice for the complete structural characterization of organic compounds; however, it is not always possible to obtain a single crystal of size and quality adequate to meet the requirements of the techniques, especially when dealing with metastable polymorphs which are often the result of solid-state phase transitions and are not sufficiently stable in ambient conditions. In those difficult cases only the powder form of the compound may be available, making powder diffraction an invaluable tool for a complete structural characterization, as proven by the steady increase in the number of structures solved *ab initio* from powder data in recent years (David *et al.*, 2006).

Nifedipine [3,5-dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate] (see Fig. 1) is a water-insoluble drug acting as a calcium channel antagonist, extensively used for the treatment of various cardio-vascular disorders (Fleckenstein, 1977; Sorkin *et al.*, 1985; Ali, 1989). Nifedipine polymorphism has been subject to detailed studies and was first described by Eckert & Mueller (1977), who report the existence of three monotropically related polymorphs, namely modifications (I), (II) and (III); modification (I) (form *A*) is stable at room temperature, while modification (II) (form *B*) and (III) (form *C*) are metastable and typically obtained from supercooling of the melt and subsequent annealing. The stable modification is that used in pharmaceutical formulations, while the other two polymorphs may appear as by-products of the fabrication process, especially when the presence of carrier molecules such as cyclodextrins or polyvinylpyrrolidone is involved (Uekama *et al.*, 1992; Hirayama *et al.*, 1994). Those findings were also confirmed by Aso *et al.* (1995) and Burger & Koller (1996), who were also able to synthesize four other solvatomorphs through crystallization from 1,4 dioxane. The physicochemical properties and thermal stability of the three nifedipine modifications were thoroughly investigated by Caira *et al.* (2003); Chan *et al.* (2004) characterized nifedipine devitrification from the melt under controlled humidity by combined FT–Raman, IR and Raman microscopic investigation, also confirming the existence of two metastable species (referred to as form β and form γ). Finally, Grooff *et al.* (2007) performed a detailed study of polymorphic transitions in the nifedipine system involving variable-temperature powder diffraction, confirming that the three polymorphs exhibit different crystal structures.

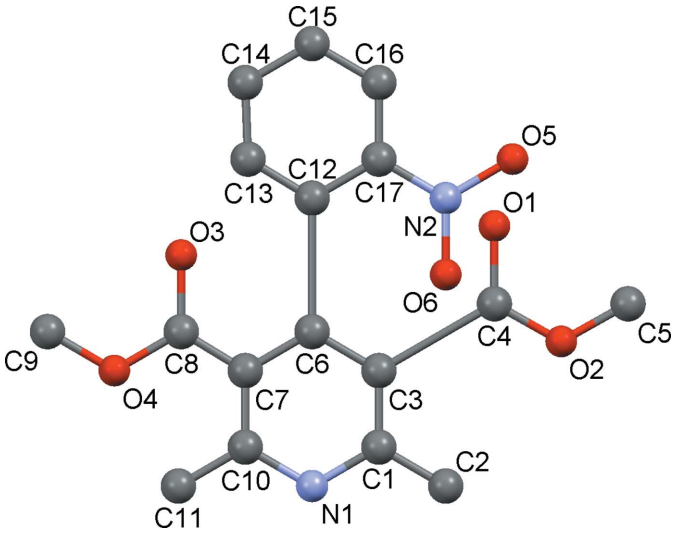

Figure 1
Nifedipine chemical diagram reporting the atom codes.

Despite considerable pharmaceutical importance, with its wide adoption as an anti-hypertensive drug, as well as extensive studies on its polymorphism, the only crystallographically characterized nifedipine form is that of the stable modification (form *A*), whose structure was solved by single-crystal X-ray diffraction (Triggle *et al.*, 1980). Recently, the structures of two solvatomorphs have been described (Caira *et al.*, 2003; Klimakow *et al.*, 2010; the latter also reports the possible indexing of a powder pattern likely belonging to form *C*); nonetheless, a complete crystallographic characterization of the two metastable nifedipine polymorphs has still to be performed.

In this work we report for the first time the crystal structure of the form *C* polymorph solved using a simulated annealing direct-space algorithm applied to high-resolution synchrotron powder diffraction data; in addition, we confirm the formation of modification *B* during the thermal annealing of both amorphous and form *C* powder samples prior to the complete crystallization of the stable phase.

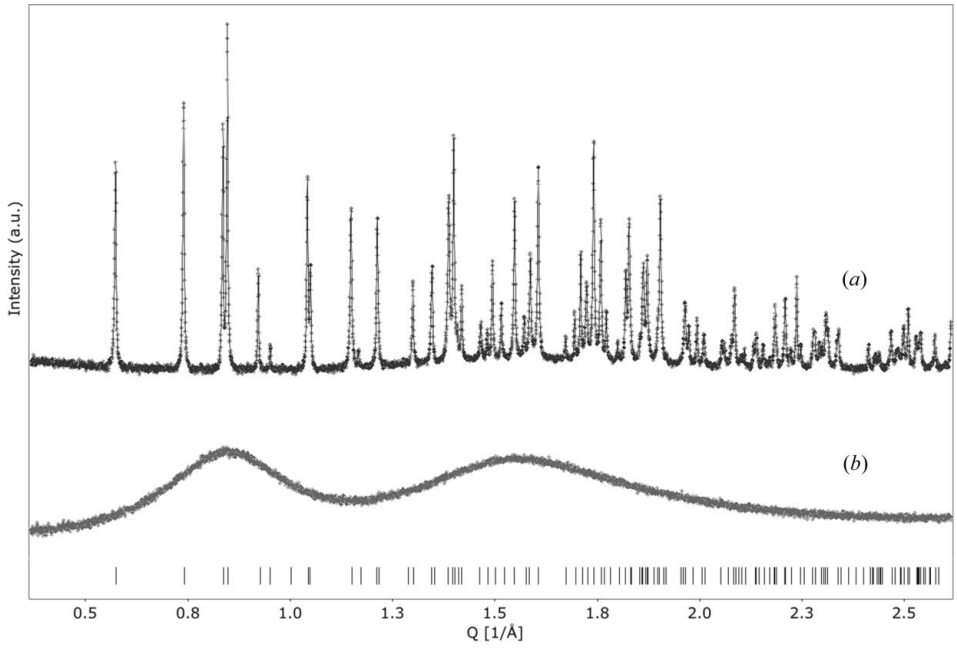

Figure 2
Powder diffraction pattern of (*a*) nifedipine form *A* (commercial powder) and (*b*) the amorphous powder obtained by fast cooling of the melted sample. Reflection marks reported on the bottom are relative to form *A*.

2. Experimental

2.1. Materials

Nifedipine form A (batch number E1372) was kindly donated by Eurand Italia. Powder diffraction data collected on the commercial product confirmed correspondence with the crystal structure of the stable form *A* as

reported by Triggle *et al.* (1980); CSD entry BICCIZ, PDF entry 02-060-4397 (Allen, 2002; Kabekkodu, 2011), space group $P2_1/c$, $a = 10.923$ (5), $b = 10.326$ (6), $c = 14.814$ (7) Å, $\beta = 92.70$ (6)°, $V = 1669.03$ (494) Å^3. No additional impurities were detected in the diffraction pattern (see Fig. 2*a*).

2.2. Synchrotron high-resolution powder diffraction

Powder diffraction experiments were performed at the Swiss–Norwegian beamline (BM01B) of the European Synchrotron Radiation Facility in Grenoble, France. The beamline is mainly designed for high-resolution powder diffraction, with the additional capability to perform combined diffraction/XAS experiments. The powder diffraction instrument consists of a two-circle goniometer equipped with six counting chains, each consisting of an Na-I scintillation counter coupled with a Si-111 analyser crystal; detectors are mounted with a 1.1° relative 2θ offset (see Fig. 3*a*). This instrumental setup allows fast data collection while maintaining at the same time an excellent intrinsic resolution (0.01° FWHM at $\lambda = 1$ Å).

Diffraction data were collected using 0.5 Å radiation and a 0.002° angular step over a 0.5–25° 2θ interval. Counting times between 10 and 200 ms per step were used for the various experiments, depending on the kinetics of the phenomena observed. Samples were loaded in a 0.7 mm capillary spinning in the axial direction to improve particle statistics. For *in situ* characterization, a hot-air blower placed under the capillary sample holder was used, with a temperature range from 298 to 1273 K (Fig. 3*b*). The instrumental calibration was performed using a NIST 640c silicon standard.

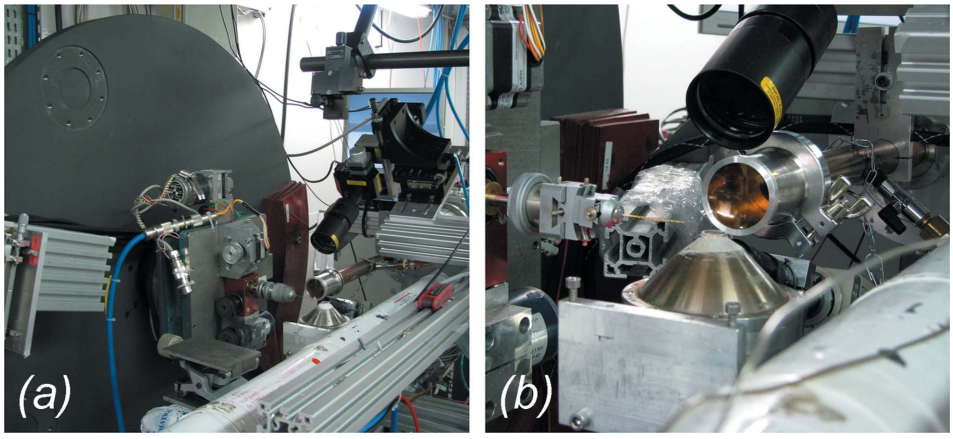

Figure 3
Experimental station at BM01B (ESRF, Grenoble) with (*a*) the powder diffractometer and (*b*) a more detailed view of the hot-air blower used during the annealing experiments.

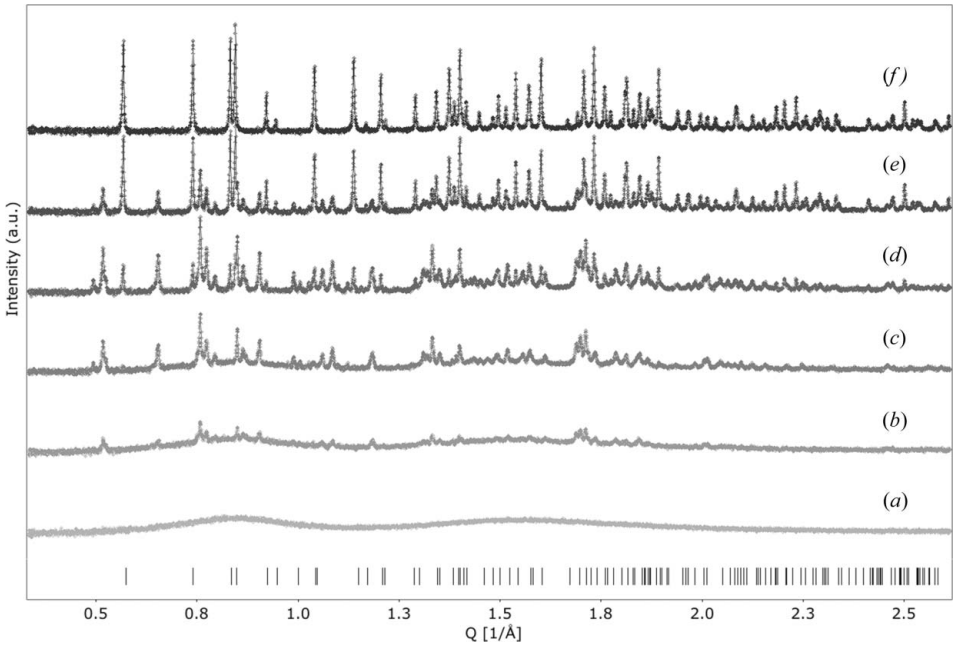

Figure 4
In situ thermal evolution of amorphous nifedipine (*a*) at 337 K showing the nucleation of the metastable polymorph *B* after 10 min (*b*), and of the stable form *A* after 30 min (*c*). After 60 min the sample has completely transformed to form *A* (*f*). Reflection marks on the bottom show peak positions relative to the stable modification.

Different sample preparation methodologies and data collection strategies were tested in an attempt to isolate the pure polymorphs and collect powder data of sufficient quality to allow a reliable *ab initio* structure solution. In a first experiment the commercial nifedipine powder (sample 1) was used without further treatments, with the goal of performing a complete *in situ* characterization of the devitrification behaviour under annealing. The sample was loaded in the capillary and heated beyond the melting point (~ 463 K), then kept at this temperature for 10 min; the Bragg peaks disappearing in the observed diffraction pattern confirmed the complete melting of the compound. The capillary was then quickly removed from the furnace and allowed to cool at room temperature (~ 298 K), inducing the formation of an amorphous glass. The sample was then reheated to 323 K (heating rate 5 K min^{-1}), then subjected to variable-temperature powder X-ray diffraction (PXRD) from 323 to 423 K in 2 K steps. A second sample (sample 2) consisting of the commercial

powder was heated *ex situ* in an electric oven to 463 K for several minutes until completely melted, then allowed to cool at room temperature. The solidified amorphous glass was then pulverized with an agate mortar and pestle, and the obtained powder subjected to variable-temperature PXRD with the same annealing schedule described for sample 1. In a final experiment (sample 3), the form *C* polymorph was obtained *ex situ* following the procedure described in Burger & Koller (1996); form *A* powder was placed on an aluminium foil and heated on a hot-plate beyond the melting temperature, then allowed to cool at room temperature; the amorphous glass thus obtained was then reheated to $\sim$ 333 K when the crystallization of the first metastable polymorph (form *B*) was observed. Once visual observation confirmed crystallization was complete, the sample was allowed to cool at room temperature to favour the form *B* $\rightarrow$ form *C* transition, visually confirmed by morphological and chromatic variations of the sample (Grooff *et al.*, 2007). The form *C* sample thus obtained was then pulverized and loaded in the capillary; high-quality powder data suitable for the *ab initio* structure solution were collected at room temperature, then the thermal evolution of the sample was studied using the annealing schedule previously described and applied to the other samples.

3. Results and discussion

3.1. *In situ* thermal behaviour of nifedipine

Nifedipine polymorphs are typically obtained starting from the amorphous form by means of a non-equilibrium devitrification process. Nucleation of form *B* crystals is induced by a thermal annealing of the amorphous phase; depending on the heating rate and the physical characteristics of the sample (solid glass or powder), a considerable variability in the nucleation temperature is observed, varying from 333 to 363 K (Aso *et al.*, 1995; Zhou *et al.*, 2003). Starting from the metastable form *B*, polymorph *C* is then obtained by rapid cooling to room temperature, while a further temperature increase will invariably produce the nucleation and growth of the stable form *A* (Grooff *et al.*, 2007).

An *in situ* characterization of nifedipine polymorphism thus presents the need to heat the stable modification above the melting point and then rapidly cool it to room temperature to obtain the amorphous state of the sample, before performing the subsequent thermal annealing treatments that induce the nucleation of the polymorphs. The relatively narrow nucleation and stability interval of the metastable forms (form *B* in particular) presents a series of experimental challenges, firstly accurate and continuous control of the sample temperature. The thermal conditioning set-up adopted during this work, based on the use of a hot-air blower heating a relatively large sample region (Fig. 3*b*), did not allow a particularly sophisticated temperature control; in fact, a considerable thermal gradient was induced along the illuminated volume of the sample, giving rise to a differential thermal history and, consequently, inconsistent crystallization behaviour along the capillary axis. On the other hand, the beam-sampling volume had to be large enough to assure adequate counting statistics during thermal evolution experiments, making it very difficult to obtain high-quality diffraction patterns of the pure polymorphs.

In the case of nifedipine commercial powder (pure form *A*, sample 1), solidification upon rapid cooling of the melt produced a discontinuous amorphous glass inside the capillary, worsening the thermal gradient issue and thus making a complete *in situ* characterization unfeasible. The amorphous powder was then obtained *ex situ*, as described in §2 (sample 2), and subjected to thermal annealing starting from room temperature; diffraction patterns were acquired every 0.5 K to follow the devitrification process. The first diffraction peaks, indicating form *B* nucleation onset, appeared at 337 K; at that point the annealing was halted and the temperature kept constant to monitor the crystallization kinetics evolution. Despite several attempts it was not possible to acquire high quality data of the pure form *B* given the strong competition with the stable form *A*, which started to nucleate before

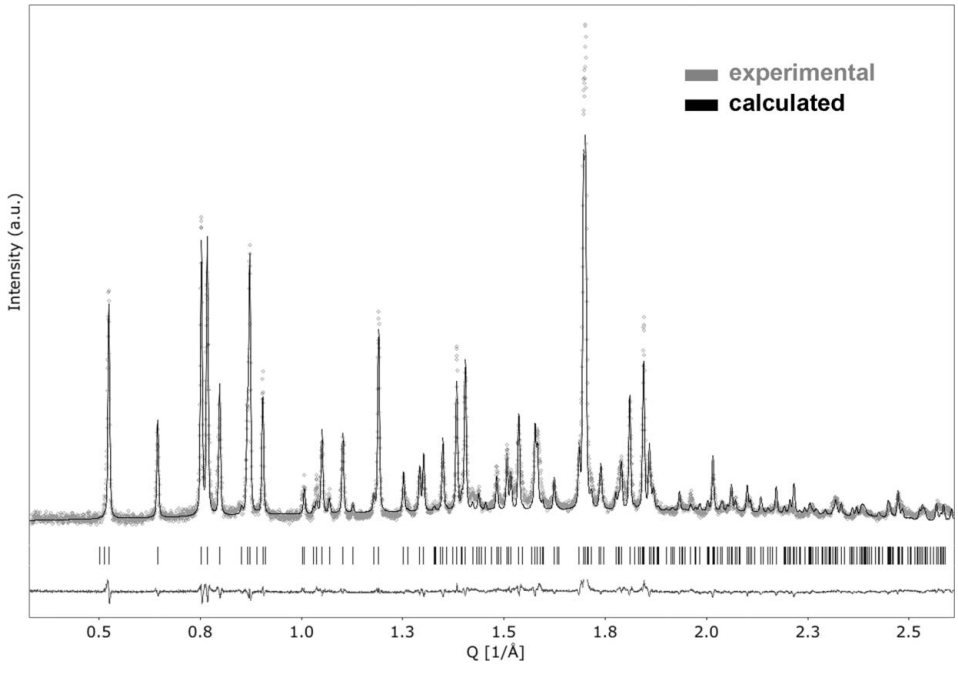

Figure 5
Experimental and calculated diffraction pattern of nifedipine form *C* (sample 3). Grey marks indicate the experimental points while the continuous black line shows the refinement result. Form *C* reflection positions as well as the difference profile are reported on the bottom of the plot.

Table 1
Crystallographic data of nifedipine form *C* after the final Rietveld refinement.

Crystal data	
Chemical formula	$C_{17}H_{18}N_2O_6$
M_r	346.34
Crystal system, space group	Triclinic, $P\bar{1}$
Temperature (K)	298
a, b, c (Å)	9.864 (1), 13.893 (9), 14.287 (3)
α, β, γ (°)	61.227 (3), 79.827 (2), 81.782 (1)
V (Å^3)	1685.5 (9)
Z	4
Radiation type	Synchrotron, λ = 0.50000 Å
Specimen shape, size (mm)	Cylinder, 14 × 0.7
Data collection	
Diffractometer	Two-theta/omega SnB diffractometer – ESRF
Specimen mounting	Capillary
Data collection mode	Transmission
Scan method	Step
2θ values (°)	$2\theta_{min}$ = 1.5, $2\theta_{max}$ = 12.0, θ_{step} = 0.002
Refinement	
R factors and goodness of fit	R_p = 0.151, R_{wp} = 0.172, R_{exp} = 0.017, R_{Bragg} = 0.151, χ^2 = 19.536
No. of data points	12 508
No. of parameters	15
No. of restraints	0
H-atom treatment	H-atom parameters not refined

the complete transformation of the amorphous phase into form *B*. Upon cooling, only the form *B* fraction transformed to form *C*, while the stable modification fraction remained unchanged, leaving again a contaminated sample. Fig. 4 reports the sample evolution at 337 K at 10 min intervals, showing evidence of form *B* nucleation (peaks at Q = 0.52, 0.65, 0.76 Å^{-1}) gradually being substituted by the crystallizing form *A* (peaks at Q = 0.58, 0.74, 0.84 and 0.85 Å^{-1}).

3.2. *Ab initio* structure solution of form *C*

Given the experimental difficulties in isolating the pure metastable polymorphs during *in situ* characterization, the *ex situ* preparation of form *C* following the procedure described in the previous paragraph (sample 3) was chosen. Once crystallized, form *C* is relatively stable at room temperature so long acquisition times were possible, allowing high-quality powder data suitable for an *ab initio* structure determination to be collected.

Diffraction spectra were acquired at room temperature (T = 298 K) over a 0.5–25.5° 2θ interval with a 0.002° step size; the counting time for each data point was 50 ms. After a careful examination to exclude formation of the stable modification, the patterns were summed together to improve signal statistics, for a total counting time of 1 s per data point (Fig. 5, grey marks). Accurate peak positions in the diffraction pattern were determined by fitting the individual reflections with the *ReX* software (Bortolotti *et al.*, 2009); the first 32 reflection positions were determined and the first 20 were input into the program *DICVOL* (Boultif & Louër, 2004). The indexing algorithm produced one solution in the triclinic crystal system with relatively high figures of merit $M(20)$ = 33.3, $F(20)$ = 280.1 (de Wolff, 1968; Smith & Snyder, 1979), and several additional results in the monoclinic space group with very low figures of merit [$M(20) < 5$]. None of the monoclinic solutions could account for all the input line positions and were thus discarded. The triclinic solution (a = 9.8698, b = 13.8935, c = 14.2862 Å, α = 61.225, β = 79.824, γ = 81.764°, V = 1686.25 Å^3) indexed all the 20 input peaks as well as the other reflections [$F(32)$ = 147.9]; moreover, the cell volume, supposing an occupancy of 4 molecules per cell, suggested an almost identical calculated density to that of the stable polymorph.

The *ab initio* structure solution was carried out with a modified version of the *ReX* software, using a direct-space approach implemented in the form of an extended search, simulated annealing algorithm (Coelho, 2000). The structural

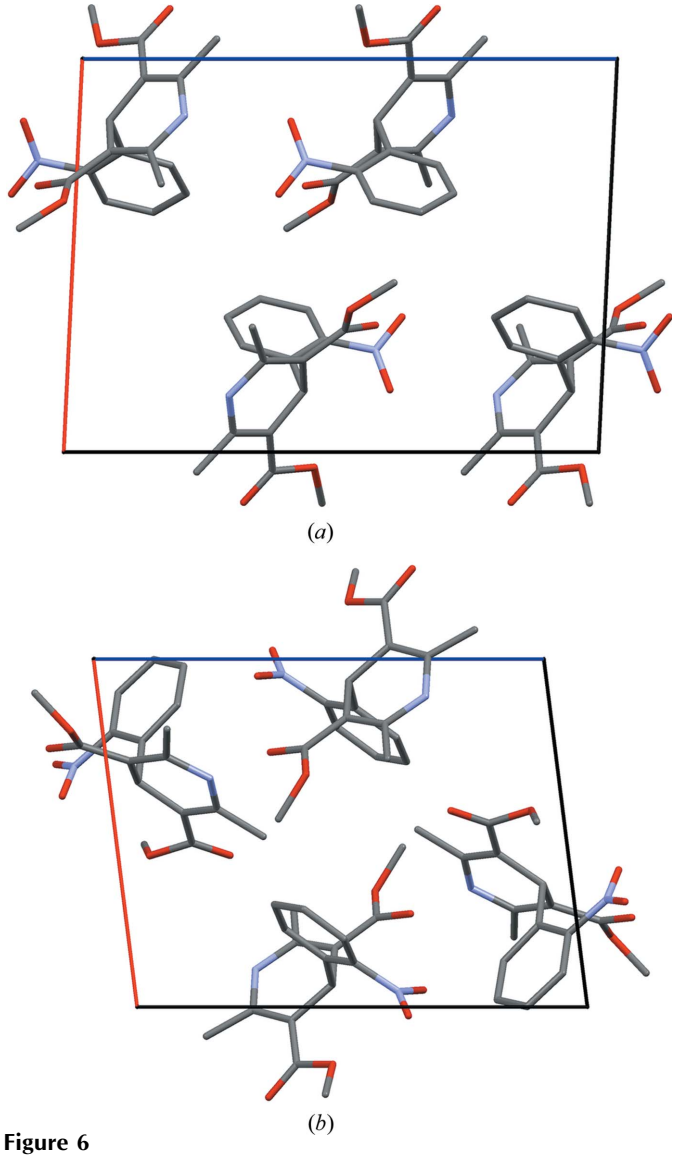

Figure 6
Comparison of the crystallographic structure of (*a*) nifedipine form *A* and (*b*) nifedipine form *C* (*c* axis orthogonal to view plane). While the molecular conformation remains substantially unchanged, the crystal packing shows important differences, with form *A* (space group $P2_1/c$) exhibiting a parallel alignment of pyridine and nitrophenyl groups, and form *C* a substantially orthogonal configuration.

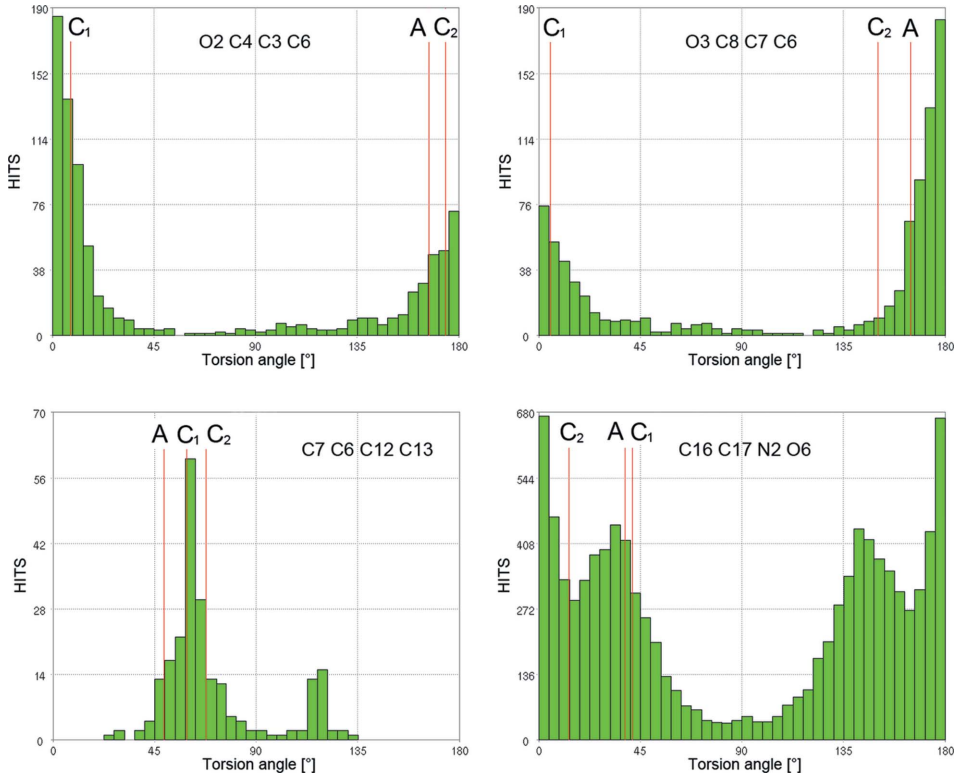

Figure 7
Comparison between torsion-angle distributions derived from the Cambridge Structural Database and observed values in nifedipine form *A* and form *C*. Values are reported for the angles formed by the pyridine fragment with the two carboxylic groups (O2—C4—C3—C6 and O3—C8—C7—C6) and the nitrophenyl group (C7—C6—C12—C13), as well as the angle between the phenyl ring and the nitro group (C16—C17—N2—O6).

optimization was attempted in the space group $P\bar{1}$, defining two independent nifedipine molecules in the asymmetric unit. For each molecule, nine geometrical parameters were defined, namely the coordinates of the centre of mass and the molecule orientation, as well as the relative orientation of the nitrophenyl group and the two carboxylate groups with respect to the main pyridine fragment. The merit function used by the solution algorithm was defined using the full powder profile; although the procedure is considerably slower with respect to working directly with integrated intensities, it avoids possible errors introduced during the profile intensity extraction in procedures like that of Pawley (Pawley, 1981) or Le Bail (Le Bail *et al.*, 1988). To maximize the convergence chance six trial runs were performed, starting each time from a random structural parameters set; each run evaluated a population of 10^6 individuals. Of the six optimization runs, four converged to a final R_{wp} value < 0.25 before the 500 000 th step, a behaviour which was considered a reliable indicator of an achieved convergence; the two other runs reached a plateau at a R_{wp} value of ~ 0.5 without further improvements. The solutions obtained from the four successful runs were compared and found to be equivalent from a crystallographic point of view, displaying differences only in the absolute positioning of the asymmetric unit inside the unit cell. The high R_{wp} solutions were, on the other hand, clearly unsound from a chemical point of view, showing overlapping molecules inside the unit cell and unreasonable bond angles.

Starting from the *ab initio* solution, the final Rietveld least-squares optimization was performed with the software *Maud* (Lutterotti *et al.*, 1999); refined parameters included an intensity scale factor and a fourth-order polynomial background, as well as unit-cell constants and average crystallite size; isotropic displacement parameters were globally refined. The final value of R_{wp} obtained was 0.172; the calculated cell volume is 1685.54 Å^3, only 1% higher than the stable modification. The experimental pattern, as well as the calculated profile and the error plot are shown in Fig. 5; a crystallographic data summary is reported in Table 1.

H-atom positions, not taken into account during the structure solution and the successive Rietveld optimization steps, were determined and added to the refined structure using the algorithm implemented in the *OpenBabel* software package (Guha *et al.*, 2006); the complete chemical structure with atomic coordinates is reported in the supporting material.[1]

The unit cell of nifedipine form *C* is shown in Fig. 6(*b*), compared with the stable modification (Fig. 6*a*) as obtained from the literature (Triggle *et al.*, 1980). The asymmetric unit contains two molecules in general positions; the most significant difference between the two polymorphic structures lies in the molecular packing. In modification *A* (space group $P2_1/c$) both pyridine and nitrophenyl rings are parallel to each other, showing a head-tail and head-head configuration; in form *C*, on the contrary, molecules are aligned in an approximately orthogonal configuration, with the pyridine groups of one molecular fragment (C_1) and the other (C_2) forming an angle of 89.13°, and the respective nitrophenyl groups slightly misaligned (83.17°).

The molecular conformation, on the other hand, is remarkably similar to that of form *A*, as well as the two solvatomorphs reported in the literature (Caira *et al.*, 2003; Klimakow *et al.*, 2010). A conformational comparison investigation was carried out through a search for similar compounds inside the CSD (Allen, 2002). Using the *Mogul*

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: KD5048). Services for accessing these data are described at the back of the journal.

Table 2
Comparison between selected dihedral angles (°) in forms *A* and *C*.

Polymorph	Form *A*	Form *C* (1)	Form *C* (2)
O2—C4—C3—C6	166.5	8.1	174.2
O3—C8—C7—C6	164.7	5.1	150.0
C7—C6—C12—C13	49.1	59.1	67.4
C16—C17—N2—O6	38.0	41.5	13.1

software (Bruno *et al.*, 2004) with an exact match search criterion ($R < 0.10$), statistical distributions were retrieved for the dihedral angles formed by the pyridine fragment with the nitrophenyl and carboxylic groups, as well as the angle between the phenyl ring and the nitro group; the distributions were then compared with the actual values observed in form *A* and form *C* (Fig. 7). The metastable polymorph exhibits values fairly close to the distribution maxima; torsion angles relative to the two carboxyl groups (O2—C4—C3—C6 and O3—C8—C7—C6) in the molecular fragment C_1 show a similar orientation to form *A*, whereas in fragment C_2 they are rotated by $\sim 180°$. Additionally, the angle between the nitrophenyl and the pyridine group (C7—C6—C12—C13) is slightly distorted with respect to the stable modification, with a 14.15° average difference. Table 2 summarizes the various dihedral angle values for the two polymorphs.

A conformational energy comparison between the two nifedipine forms was carried out using *ab initio* methods. Single-point energy calculations were performed at the B3LYP/6-31G* level of theory using the software *GAMESS* (Schmidt *et al.*, 1993); the obtained average energy for form *C* shows a moderate 18.02 kJ mol^{-1} increase with respect to the stable polymorph, suggesting a rather stable conformational equilibrium.

The form *C* sample, structurally characterized as previously described, was finally subjected to a thermal annealing process starting from room temperature (298 K) up to the complete crystallization of the stable modification (Fig. 8). Diffraction spectra were collected at 1 K intervals to closely follow the solid-state evolution of the material. Form *C* was stable up to 328 K, after which new diffraction peaks belonging to form *B* (Q = 0.52, 0.65 and 0.76 Å^{-1}) started to appear in the diffraction pattern. Even in this case, however, it was not possible to avoid the contamination of the sample by the stable form *A*, which started to nucleate immediately after (peaks at Q = 0.58, 0.74, 0.84 and 0.85 Å^{-1}). Reflections belonging to form *B* started to disappear at 358 K, when the sample was almost completely composed of the stable modification.

4. Conclusions

We reported for the first time the structure of nifedipine form *C*, solved by means of *ab initio* direct-space methods applied to synchrotron powder diffraction data. The polymorph crystallizes in the space group $P\bar{1}$, with a cell volume nearly equal to that of the stable form; in addition, the internal conformation of the nifedipine molecules resembles very closely that observed in the stable form, with comparable bond lengths and bond angles. On the other hand, the molecular packing differs substantially, with molecules orthogonally aligned with respect to each other.

The existence of another transient metastable polymorph (form *B*) with a different crystal structure is confirmed; its occurrence can be observed during thermal annealing from room temperature of the form *C* polymorph as well as the amorphous form. Unfortunately, it was not possible to collect good quality diffraction data of form *B*, which is stable only in a very limited temperature interval. The authors believe that such fast transformation kinetics could be successfully followed using the new generation of real-time multiple strip (RTMS) detectors, which when coupled to a high brilliance synchrotron source can provide an almost real-time sample monitoring while maintaining the high instrumental resolution needed for advanced structural investigations.

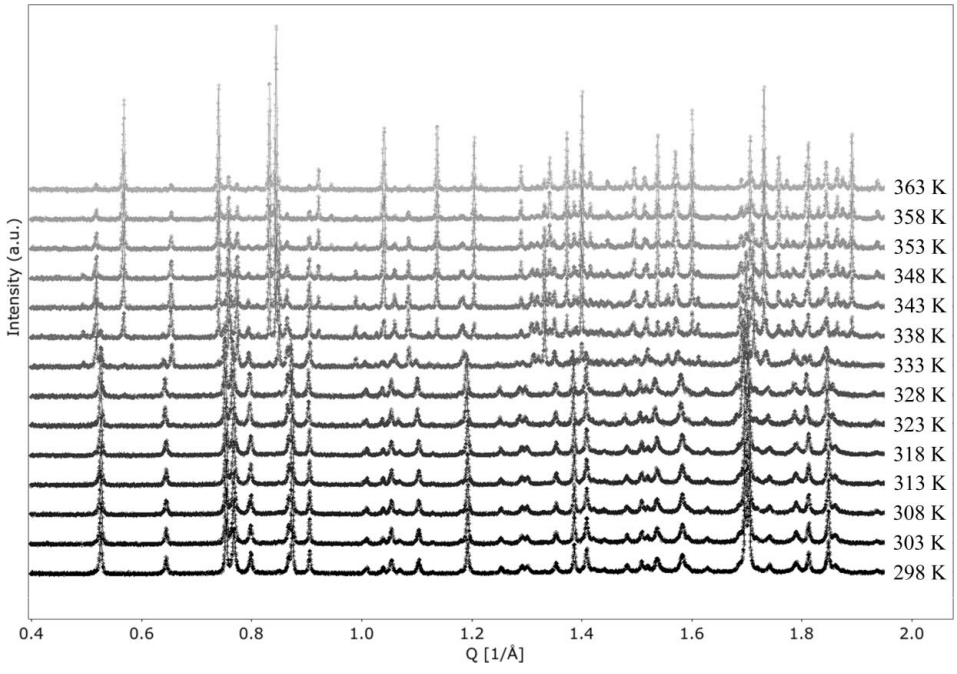

Figure 8
In situ thermal evolution of nifedipine form *C* (sample 3) from 298 to 363 K. Form *C* remains stable up to 328 K, when peaks belonging to both form *B* and form *A* start to appear. Transformation to the stable modification *A* is almost complete at 363 K.

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