Structural study of nifedipine polymorphs by means of high-resolution powder diffraction

Summary

Aim of the experiment was to carry out an exhaustive, in-situ structural study of Nifedipine (C17H18N2O6) polymorphism and solid-state phase transitions. Powder diffraction experiments were performed at the Swiss-Norwegian beamline (BM01B), whose experimental setup allows the collection of high resolution data considerably fast. The principal outcome of the experiment was the determination of the previously unknown crystal structure of the metastable form "C" polymorph of Nifedipine, obtained by means of direct space techniques. The polymorph crystallizes in the P-1 space group 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. The full results are reported in Bortolotti et al. 2011. Additionally, in-situ thermal characterization of the 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 due to its very limited stability interval.

Experimental procedure

Diffraction data was collected using 0.5 Å radiation and a 0.002° angular step over a 0.5° – 25° 2-theta interval. Counting times between 10 and 200 ms/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 25°C to 1000°C. The instrumental calibration was performed using a NIST 640C silicon standard.

Different sample preparation methodologies and data collection strategies were tested in the attempt to isolate the pure polymorphs and collect powder data of sufficient quality to allow a reliable *ab-initio* structure solution. In-situ experiments were afflicted by some difficulties, first of all the impossibility to mantain a stable temperature along the whole capillary length. Despite this, an interesting qualitative evaluation of the thermal evolution of the Nifedipine system was obtained, and useful information about the temperature stability intervals of the various polymorphs were collected.

For the high-resolution experiment, the form C polymorph was obtained ex-situ following the procedure descripted in Burger and Koller (1996). The form C sample so obtained was then pulverized and loaded in the capillary; high quality powder data suitable for the *ab-initio* structure solution was collected at room temperature, then the thermal evolution of the sample was studied.

Diffraction spectra were acquired at room temperature (T=25 C) over a 0.5-25.5° 2-theta interval with a 0.002° step size; counting time for each data point was 50ms. 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 second per data point.

Accurate peak positions in the diffraction pattern were determined by fitting the individual reflections and then input into DICVOL (Boultif & Louer 2004). The crystal cell was indexed as triclinic with cell parameters a= 9.8698 Å, b=13.8935 Å, c=14.2862 Å, α= 61.225°, β= 79.824°, γ= 81.764°, vol=1686.25 $Å^3$.

The *ab-initio* structure solution was carried out with a modified version of the ReX software (Bortolotti et al. 2009), using a direct space approach implemented in the form of an extended search Simulated Annealing algorithm. Starting from the *ab-initio* solution, the final Rietveld least squares optimization was performed with the software Maud (Lutterotti 1999), with a final obtained value of R_{wp} of 0.172 (Figure 1).

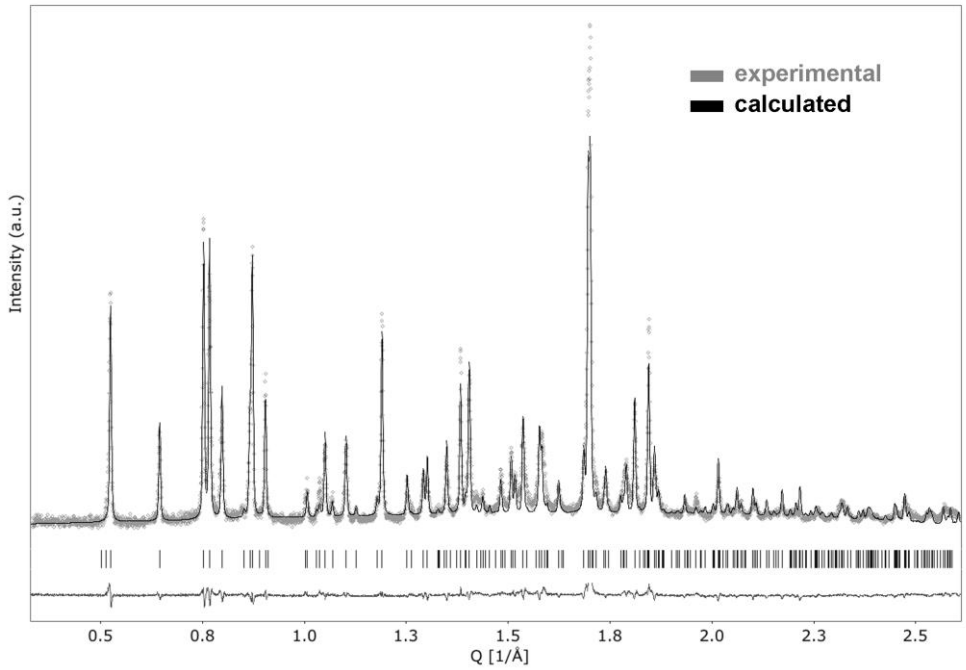

Figure 1

The unit cell of nifedipine form-C is shown in Figure 2 (b), compared to the stable modification (Figure 2 (a)) as obtained from the literature (Triggle 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 P21/c), both pyridine and nitrophenyl rings are parallel to each other, showing a head-tail and head-head configuration, respectively; in form C, on the contrary, molecules are aligned in an approximate 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 modification 1.

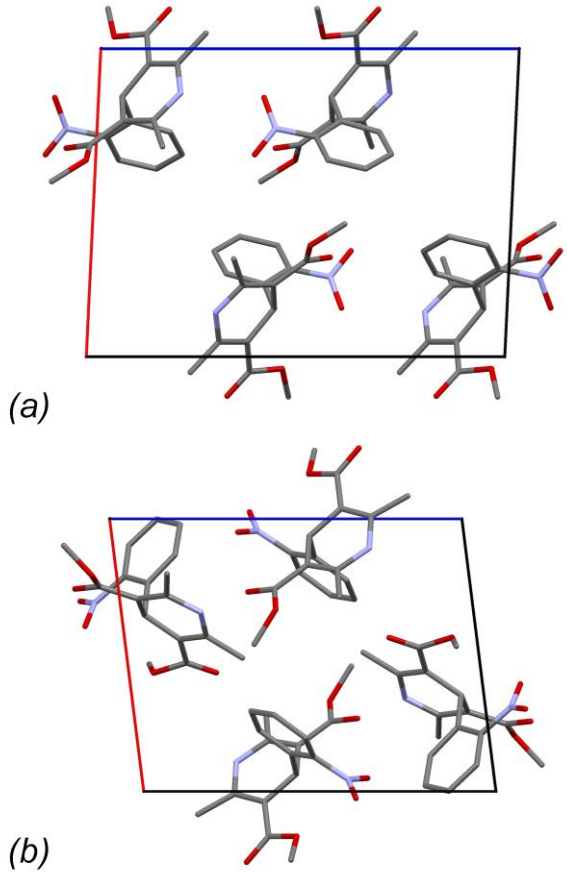

Figure 2

References

Bortolotti, M., Lutterotti, L. & Lonardelli, I. (2009). *J. Appl. Cryst.* **42**, 538–539.

Bortolotti M., Lonardelli I. and Pepponi G. - Acta Cryst. (2011). B67, 357–364

Boultif, A. & Louer, D. (2004). *J. Appl. Cryst.* **37**, 724–731.

Burger, A. & Koller, K. (1996). *T. Sci. Pharm.* **64**, 293–301.

Lutterotti, L., Matthies, S., Wenk, H. R. (1999). *Proceeding of the Twelfth International Conference on Textures of Materials (ICOTOM-12)*, Vol. 1, 1599.

Triggle, A. M., Shefter, E., Triggle, D. J. (1980). *J. Med. Chem.*, **23** (12), pp 1442–1445.