Polymorphic gabapentin: thermal behaviour, reactivity and interconversion of forms in solution and solid-state†

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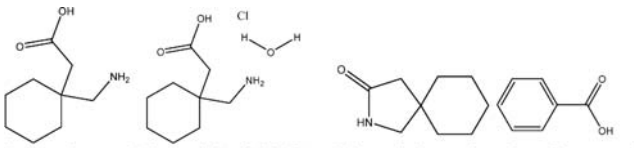
Received (in Montpellier, France) 9th June 2008, Accepted 31st July 2008
First published as an Advance Article on the web 3rd September 2008
DOI: 10.1039/b809662g

The various crystal forms of the neuroleptic drug gabapentin have been investigated, and in some cases re-investigated, by a combination of differential scanning calorimetry, hot stage microscopy and variable temperature powder diffraction methods in order to establish the relative stability of both its anhydrous and hydrated forms. A series of steps involving slurrying, heating, dehydration and reaction with vapours of HCl have been performed. In this latter case, it has been possible to show that the reaction with HCl vapour leads to the same product as that obtained in solution. In slurry experiments in the absence of water, the most stable form, Form II, is invariably obtained, whereas in water, the slurry leads to the conversion of all crystal forms to the hemihydrated Form I. The conditions for the solid-state formation of the gabapentin-lactam dehydration product have been analysed. Co-crystal formation has also been attempted. In the course of one such experiment, 1 : 1 co-crystals of gabapentin-lactam and benzoic acid were obtained.

Introduction

The amino acid gabapentin [1-(aminomethyl) cyclohexane acetic acid, Neurontin®] is a neuroleptic drug that is prescribed, usually in combination with other medication, for the prevention of seizure in people suffering from seizure disorders, and for the treatment of some mood disorders, anxiety and tardive dyskinesia.[1–8] Many papers have been published in recent years on conformational studies of gabapentin-containing peptides,[9] stereochemistry,[10] and cyclization reactions involving gabapentin[11] and transition metal (Ru, Os and Ir) catalysts.[12] Gabapentin is known as its hemihydrated form[13,14] and in various polymorphic modifications of its anhydrous form.[13,15–20] A gabapentin hemisulfate hemihydrate form has also been published that is isomorphous to the gabapentin hydrochloride hemihydrate.[21] Recently, a salt of gabapentin with oxalic acid has also been characterized.[22] Some of us have also shown that gabapentin can be used as a ligand in Cu and Zn complexes.[23]

In this paper we report the results of our studies on the thermal behaviour and interconversion between the different polymorphic and solvate forms of gabapentin in solution and in the solid-state. We also take the opportunity to describe the first example of a co-crystal involving gabapentin-lactam and benzoic acid.



Gabapentin Gabapentin hemichloride Gabapentin-lactam:benzoic acid co-crystal

Results and discussion

Before proceeding with the description of the calorimetric and diffraction experiments carried out on gabapentin, it is necessary to establish a consistent nomenclature of the known forms of the compound.

Gabapentin is known in different forms, which have been the object of many patent applications and issued patents. The nomenclature is not uniform and different papers refer to different forms, but make use of the same name. Hereafter, a short description of the known forms are reported and a uniform nomenclature is proposed. Only one hydrate form, labelled Form I, is known[14] to date, while Form II is the anhydrous commercial form.[20] The crystal structures of these forms are present in the Cambridge Structural Database (CSD), with the refcodes QIMKOM for Form I at −120 °C,[13] and QIMKIG and QIMKIG01 for Form II at −120 °C[13] and RT,[10] respectively. A new form, which we have labelled Form III, has been described by Pesachovich *et al.*,[19] and its crystal structure has recently been reported by Reece and Levendis as form γ.[15] A patent by Chen *et al.*[18] describes a new form of gabapentin named dehydrated A, which is

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† Electronic supplementary information (ESI) available: Synthesis and X-ray characterization. CCDC 697246–697248. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b809662g

consistent with form β reported by Reece and Levendis,[15] hereafter labelled Form IV. The choice of this nomenclature is also due to the fact that, while this manuscript was in preparation, containing the X-ray characterizations of forms III and IV, both at low and room temperature,‡, the paper by Reece and Levendis appeared as an online article.[15] Another crystalline form of gabapentin has been described by Lladó *et al.*,[17] but its powder pattern is very similar to that of Form IV. In the international patent application by Kumar *et al.*,[16] the reported form of gabapentin is probably a mixture of Forms III and IV. In all the characterized forms of gabapentin, the molecule crystallizes as a zwitterion.

DSC and hot-stage experiments on gabapentin polymorphs

In this section, we illustrate the results of our thermal experiments on Forms II, III and IV, and shed light on the solid-state reaction leading to the formation of gabapentin-lactam as a result of a dehydration process.

In the first heating cycle, Form II shows an endothermic peak at 158 °C (onset, Fig. 1), while in the second heating cycle, the endothermic peak is at 87 °C, thus representing the melting point of gabapentin-lactam.[24] Melting of the gabapentin-lactam obtained from the first DSC heating cycle was also observed by hot-stage microscopy at 89 °C (see Fig. 1B). The formation of gabapentin-lactam was not surprising, and it is known that gabapentin is unstable in aqueous solutions and undergoes an intramolecular dehydration reaction to yield the lactam.[25] The formation of gabapentin-lactam has also been observed in the solid-state.[24] Therefore, the endothermic peak present in the first heating cycle does not correspond to the melting of gabapentin, but instead covers several events: cyclization, release of water and melting of gabapentin-lactam. These events could not be separated, even with a slow scanning rate.

Form III shows a similar thermal behaviour, with a broad endothermic peak at 165 °C, which is again due to the cyclization process with the formation of gabapentin-lactam, water release and the melting of the gabapentin-lactam. In agreement with the DSC traces, these events were also observed in a capillary at 157.2 °C for Form II and at 163.8 °C for Form III.

As noted above, the thermodynamic Form II undergoes the reaction at a slightly lower temperature than the metastable Form III. Since the two forms exhibit a similar conformation in the solid-state, the different behaviour might be explained by the slightly different pattern of hydrogen bonds in their crystal structures.[15]

Several attempts to produce pure Form IV in a reasonable quantity to be used in DSC measurements were not successful. A DSC trace of a mixture of Forms III and IV (as provided by ZaCh System) shows two endothermic peaks at 154.7 and 167.1 °C (onset, see Fig. 2). The two peaks can be attributed to the melting of gabapentin-lactam as a result of the cyclization/water loss process for Forms IV and III, respectively. This is in agreement with a hot-stage microscopy experiment on single crystals of Form IV isolated within an oil drop. Fig. 3 clearly shows the release of water as gas bubbles in the temperature range 152–155 °C, immediately followed by melting of the gabapentin-lactam thus formed.

The unique presence in crystals of Form IV of an intramolecular N–H···O hydrogen bond, associated with a smaller number of intermolecular hydrogen bonds with respect to the other two forms, must be responsible for the lower reaction temperature observed.[15]

DSC and variable temperature X-ray powder diffraction measurements on all forms did not indicate any phase transformations before the reaction temperature.

‡ Single crystal data at room temperature for Forms III and IV as well as for gabapentin-lactam:benzoic acid co-crystal at 150 K have been deposited in the CSD.†

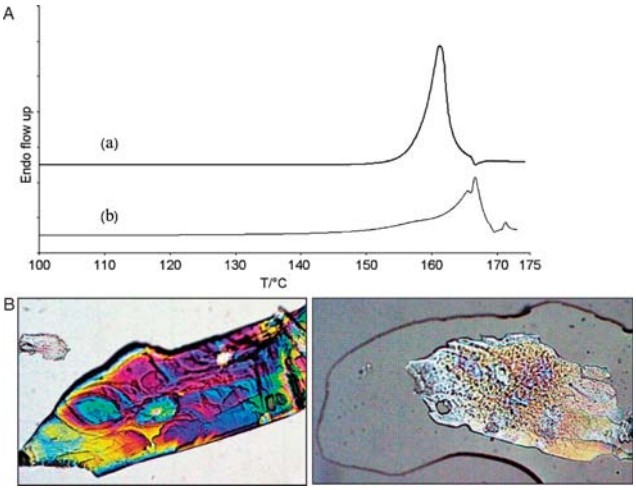

Fig. 1 (A) DSC traces (open pan) of gabapentin (a) Form II, with an onset temperature = 158.0 °C and a peak temperature = 161.1 °C, and (b) Form III, with an onset temperature = 165.0 °C and a peak temperature = 166.6 °C. (B) Hot-stage microscopy of crystalline gabapentin-lactam (left), as obtained in the first DSC heating cycle of gabapentin, showing melting at 89 °C (right).

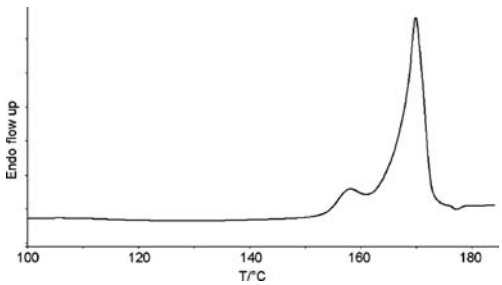

Fig. 2 DSC trace of a mixture of gabapentin Forms III and IV. The onset temperatures are 154.7 and 167.1 °C for the first and second endothermic peaks, respectively.

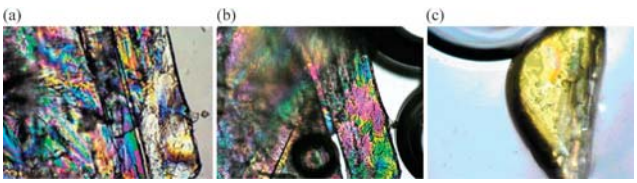

Fig. 3 Hot-stage microscopy on gabapentin Form IV crystals (preserved in Fomblin oil): (a) A single crystal at 32 °C, (b) the evolution of water bubbles at 153 °C and (c) the complete melting of the gabapentin-lactam at 157 °C (amplification ×100).

Thermodynamic stability at room temperature: slurry experiments

Slurry experiments were carried out to characterize the thermodynamic forms at room temperature (Scheme 1). Form II, Form III, and a mixture of Form III and IV (as provided by ZaCh System) were partially dissolved in methanol, and stirred at room temperature for 5 d. After this time, the solid was filtered off and characterized by X-ray powder diffraction. In all cases, the diffractograms were consistent with Form II. When water was used instead of methanol, the solid turned out to be exclusively Form I. These results are in keeping with the idea that Form II is the most stable anhydrous form, while Form I is more stable in the presence of water.

Experiments of stability under different humidity conditions

Gabapentin Forms II and III, plus a mixture of Form III and IV, were exposed to 50 and 100% relative humidity (RH) conditions at room temperature for 7 d, and the possible conversion to a different phase was checked by X-ray powder diffraction (Scheme 2). Form II kept at 50% RH was stable, while Form III, and the mixture of Forms III and IV, quantitatively transformed into Form II. At 100% RH, Forms II and III, and the mixture of Form III and IV, all transformed into Form I.

Grinding and kneading experiments

Forms II and III, and a mixture of Forms III and IV, were manually ground for 15 min, and the powders analyzed by X-ray powder diffraction (Scheme 3). The diffractogram of Form III after grinding shows new peaks, which are characteristic of Form II. The transformation could be accelerated, and complete conversion to Form II observed after 10 min by kneading, *i.e.* by grinding Form III in the presence of a non-stoichiometric amount of solvent (see the Experimental section), in this case ethanol (see Fig. 4).

The mixture of Forms III and IV converts quantitatively into Form II by grinding

Form II does not transform upon grinding, nor after kneading with a series of different solvents, in particular acetonitrile, chloroform, DMSO, methanol, water, hexane and ethyl acetate (see Fig. 5).

Dehydration experiments

Dehydration of Form I leads to formation of mixtures of pure or mixed anhydrous phases, depending on the experimental conditions. Our experiments (Scheme 4) were conducted at temperatures equal to or lower than 100 °C, as it is known that high temperature leads to formation of gabapentin-lactam.[24] In all cases, the formation of gabapentin-lactam has been excluded on the basis of the XRPD patterns. We have found that Form I heated at 100 °C under vacuum leads to formation of a mixture of Forms II, III and IV, while at ambient pressure, the formation of Form II is not observed (see Fig. 6).

Slurry in methanol:

II → II III → II III + IV → II

Slurry in water:

II → I III → I III + IV → I

Scheme 1

50% RH:

II → II III → II III + IV → II

100% RH:

II → I III → I III + IV → I

Scheme 2

Grinding and kneading:

II → II III → II III + IV → II

Kneading:

II → II

Scheme 3

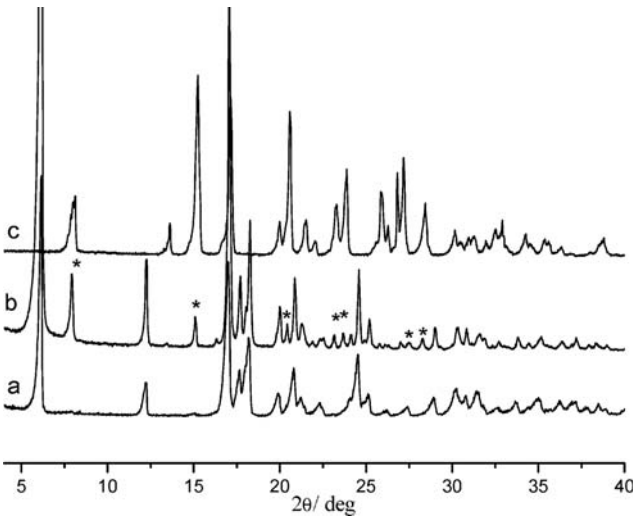

Fig. 4 XRPD patterns of (a) Form III, (b) Form III after grinding (stars indicate peaks of Form II) and (c) Form III after kneading with ethanol. In this case, complete conversion into Form II was achieved.

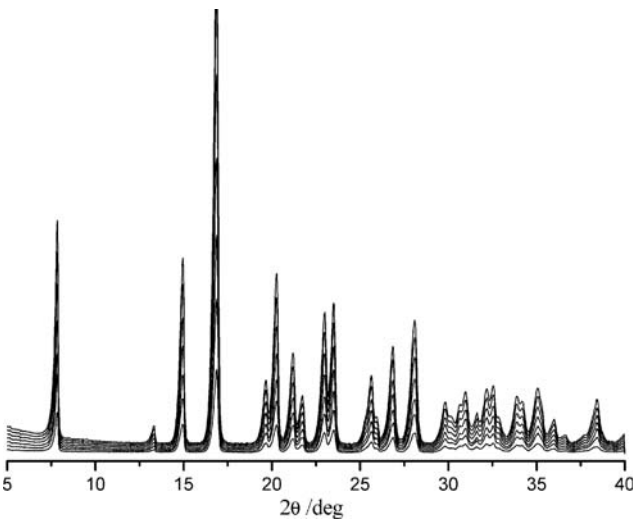

Fig. 5 Comparison of the powder patterns of Form II after kneading with a small amount of different solvents.

100°C for 2 hours under vacuum .....Form I → Forms II + III + IV

100°C for 30 minutes .....Form I → Forms III + IV

desiccator with silica gel for 3 days.....Form I → Forms IV (not pure)

desiccator at 50°C for 3 days .....Form I → Form III

Scheme 4

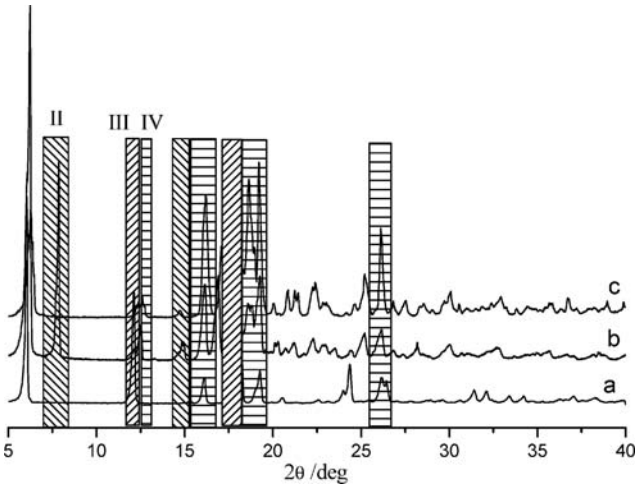

Fig. 6 A comparison of the XRPD patterns for (a) Form I (starting compound), (b) the mixture obtained by heating Form I at 100 °C under vacuum and (c) the mixture obtained by heating Form I at 100 °C at ambient pressure.

Milder conditions, such as keeping the hydrated form in a desiccator with silica gel for 3 d, turned Form I into Form IV (possibly with a tiny amount of Form III) (see Fig. 7).

On the contrary, pure Form III was obtained when gabapentin Form I was left for 3 d at 50 °C, at ambient pressure, in a closed flask (see Fig. 8).

The formation of pure Form IV seemed not to be possible by drying methods. Furthermore, Form IV was unstable and easily transformed with time into Form II or III, or a mixture of the two.[18]

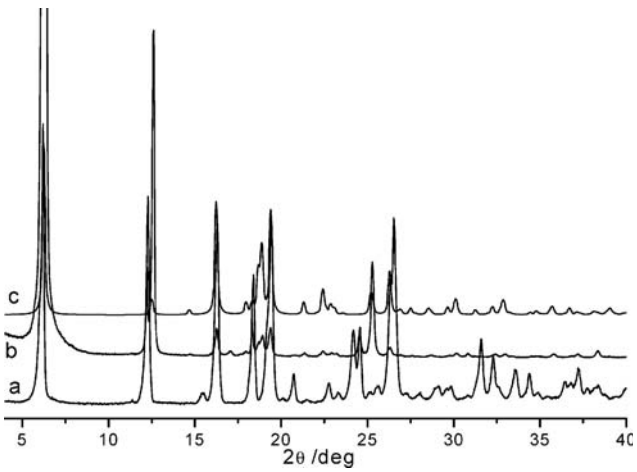

Fig. 7 A comparison of the experimental XRPD patterns for (a) Form I (starting compound), (b) the powder obtained by drying Form I in a desiccator and (c) the calculated powder pattern of Form IV.

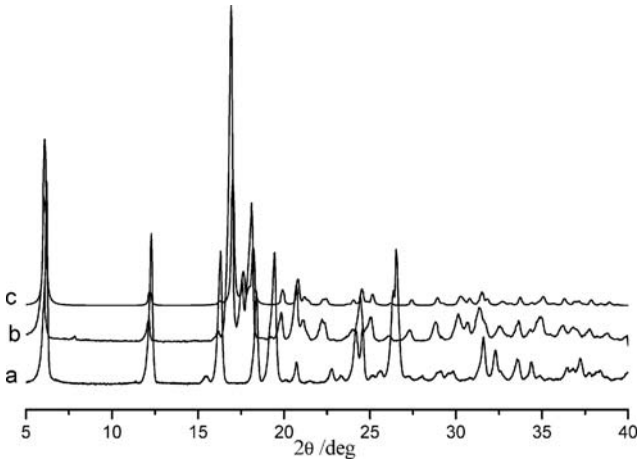

Fig. 8 Form I, after (a) 3 d at 50 °C, transforms completely into Form III ((b) experimental pattern, (c) calculated pattern).

The reaction of solid gabapentin with vapours of HCl

As we have discussed in a series of previous publications, solid–gas reactions are conceptually very similar to solid–vapour processes.[26–29] Thus, as it is possible to obtain new anhydrous polymorphic forms of a given molecule by the dehydration of a solvate, it is possible, at least in principle, to obtain new crystal forms, or the interconversion between otherwise non-interconverting crystals, *via* solid–gas reactions.

With this idea in mind, we attempted the reaction of solid gabapentin with vapours of aqueous HCl. Gabapentin Form II reacted with vapours of HCl to yield gabapentin hydrochloride hemihydrate, whose structure is known.[10] The thermogram of gabapentin hydrochloride hemihydrate showed a loss of weight of about 3% in the range 90–120 °C, which corresponds to a partial release of water (the percentage of water calculated on the basis of the chemical formula is 4.4%), while complete dehydration was reached only at a higher temperature (Fig. 9). The DSC trace and variable temperature X-ray powder diffraction clarify the behaviour of gabapentin hydrochloride hemihydrate at high temperatures. In the DSC curve (see Fig. 10(a)), two endothermic peaks are present between 90 and 125 °C. The first peak can be attributed to the same *partial* loss of water as observed in the TGA, while the second sharp peak corresponds to the loss of residual water, accompanied by incongruent melting (as frequently observed in solvates when DSC experiments are performed in an open pan[30]) and recrystallization of the

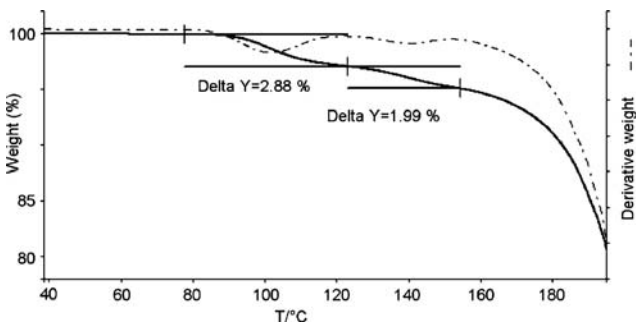

Fig. 9 The TGA trace of gabapentin hydrochloride hemihydrate.

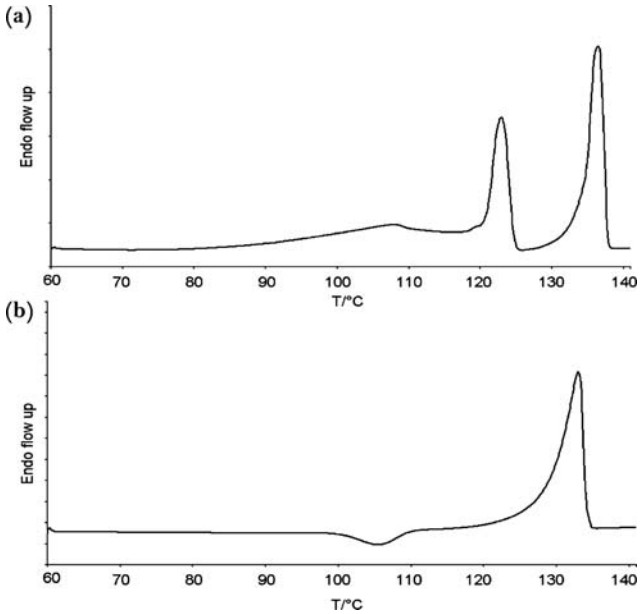

Fig. 10 DSC traces of gabapentin hydrochloride hemihydrate: (a) In the first heating cycle, the two endothermic peaks at 90 and 125 °C can be attributed to the partial loss of water and loss of residual water, respectively, the second event being accompanied by incongruent melting and recrystallization of GBP·HCl I, which melts at 134 °C (onset). (b) In the second heating cycle, melting of GBP·HCl II is observed at 129 °C (onset).

anhydrous gabapentin hydrochloride (which we shall call GBP·HCl I). This is confirmed by the fact that the XRPD pattern collected at 125 °C differed from the one measured at 90 °C (see Fig. 12). At 134 °C (onset, Fig. 10(a)) GBP·HCl I melted; recrystallization from the melt observed upon cooling resulted in the formation of a new polymorphic form of anhydrous gabapentin hydrochloride (GBP·HCl II), which shows significant differences in its powder pattern with respect to the high temperature form of anhydrous gabapentin hydrochloride (see Fig. 11). GBP·HCl II melted at a lower temperature, 129 °C (onset, Fig. 10(b)). The shallow exothermic peak observed in the DSC trace of GBP·HCl II might be due to recrystallization of the residual amorphous sample, although we cannot completely rule out the possibility of a monotropic transition to a third anhydrous phase.

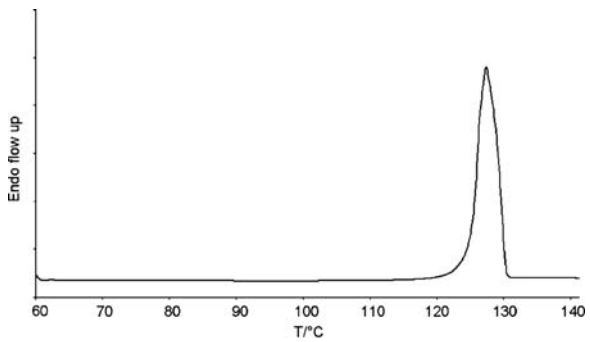

Fig. 12 The DSC trace of gabapentin hydrochloride hemihydrate in a closed pan.

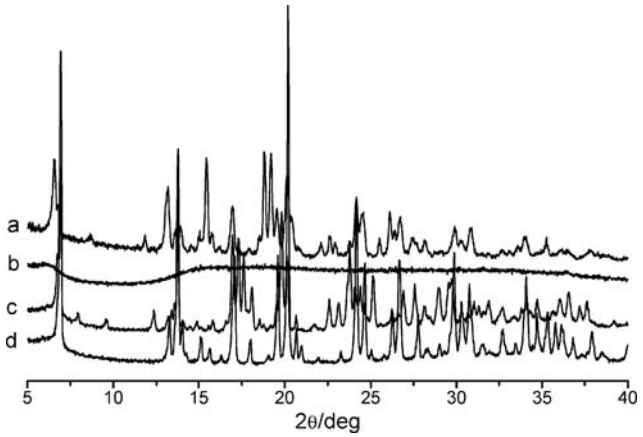

Fig. 11 Variable temperature XRPD measurements on a sample of gabapentin hydrochloride hemihydrate, showing the phase transition to anhydrous GBP·HCl I and recrystallization of GBP·HCl II from the melt: (a) GBP·HCl II at RT, (b) melt at 145 °C, (c) GBP·HCl I at 125 °C and (d) gabapentin hydrochloride hemihydrate at 90 °C.

It is worth noting that the anhydrous form GBP·HCl I when left at room temperature readily absorbs water from the atmosphere and converts back to gabapentin hydrochloride hemihydrate. On the contrary, the anhydrous form, GBP·HCl II (obtained by recrystallization from the melt), is stable in the air at ambient temperature.

A DSC measurement on gabapentin hydrochloride hemihydrate in a closed pan shows only one endothermic peak at 125 °C (onset, Fig. 12) due to congruent melting.[30] The XRPD pattern of the solid obtained by recrystallization from the melt corresponds to the pattern of the starting gabapentin hydrochloride hemihydrate.

The crystal structure of a gabapentin derivative

Gabapentin-lactam (GBP-L) is a derivative of gabapentin. Recently, GBP-L revealed some benefits over gabapentin, because of a pronounced neuroprotective activity, neurotrophic effects[31] and the absence of sedation effects.[32,33]

In this section, we describe the serendipitous discovery of the first co-crystal of gabapentin-lactam. In an attempt to obtain co-crystals of gabapentin and benzoic acid, we recovered crystals that turned out to be the 1 : 1 co-crystal gabapentin-lactam:benzoic acid (Fig. 13).

The main conformational difference of gabapentin-lactam in the co-crystal, with respect to gabapentin-lactam in its pure

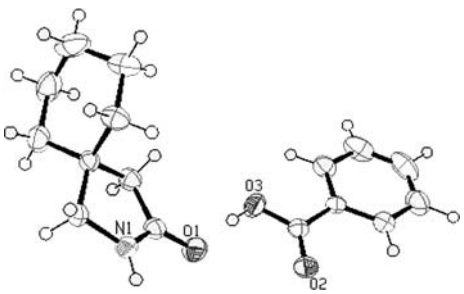

Fig. 13 ORTEP diagram of the co-crystal gabapentin-lactam:benzoic acid determined at 150 K. Ellipsoids are set at 50% probability.

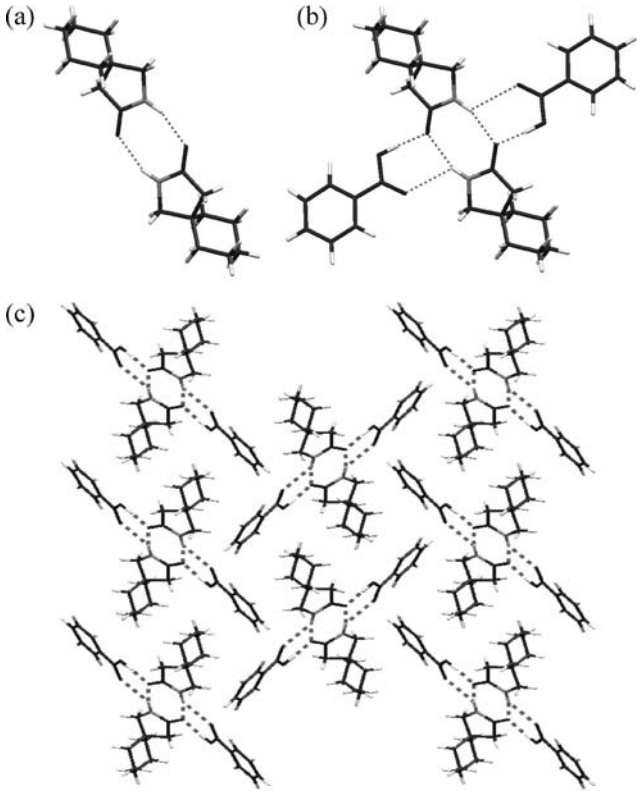

Fig. 14 The gabapentin-lactam:benzoic acid co-crystal: (a) Dimers formed by gabapentin-lactam molecules interacting *via* NH···O hydrogen bonds, (b) the tetramers formed *via* $NH\cdots O_{Bz}$ and $O\cdots HO_{Bz}$ hydrogen-bonding interactions of one dimer with two benzoic acid molecules, and (c) rows of tetramers viewed along the b-axis.

crystals, is the relative position of the five membered ring—in the equatorial position in the former and in the axial position in the latter. Gabapentin-lactam and benzoic acid form hydrogen-bonded tetramolecular aggregates in the crystal, with a pair of gabapentin-lactam molecules linked *via* N–H···O interactions ($N\cdots O_{CO}$ = 2.967(4) Å). Interestingly, these dimers are also observed in the crystal structure of gabapentin-lactam.[10] The gabapentin-lactam dimers (Fig. 14(a)) interact with benzoic acid molecules, giving rise to tetramers (Fig. 14(b)). The hydrogen from the amide group acts as a double donor, interacting also with the C═O group of benzoic acid ($N(–H)\cdots O_{CO}$ = 3.161(4) Å). The hydrogen atoms from the hydroxyl group of the benzoic acid molecules act as donors to the C═O group of the lactam ($O_{OH}(–H)\cdots O_{CO}$ = 2.572(4) Å). Along the b-axis, the tetramers organize themselves into vertical rows (Fig. 14(c)), and in each line, the tetramers show a *ca.* 80° rotation compared to the tetramers in the next row.

Conclusions

In this paper, we have characterized the crystal forms of gabapentin by means of calorimetric and diffraction techniques. We have been able to show that the polymorphic and hydrated crystal forms of this neuroleptic drug convert to the most stable Form II in slurry experiments in the absence of water, while a slurry in water leads invariably to hydrated crystals. The dehydration of Form I, on the other hand, leads to Form II, which reversibly uptakes water in humid conditions. We have also explored the reactivity of gabapentin towards vapours of HCl, showing the formation of the hydrated hydrochloride system, which can also be obtained from solution. The conditions for the solid-state formation of the gabapentin-lactam dehydration product have also been analysed. Finally, we have shown that a 1 : 1 co-crystal of gabapentin-lactam and benzoic acid could be prepared by the direct reaction of gabapentin and benzoic acid in a serendipitous attempt to prepare co-crystals of gabapentin itself.

Experimental

Gabapentin Forms I, II and III, the mixture of Forms III and IV, and gabapentin hydrochloride hemihydrate were supplied by ZaCh System. All solvents were purchased from Aldrich and used without further purification.

Slurry experiments

A 150 mg sample of gabapentin Forms II or III, or a mixture of Forms III and IV, was suspended in methanol and stirred in a closed vessel for one week. In all cases, X-ray powder diffraction confirmed complete conversion to Form II.

A 150 mg sample of gabapentin Forms II or III, or a mixture of Forms III and IV, was suspended in water and stirred in a closed flask for one week. In all cases, X-ray powder diffraction confirmed complete conversion to Form I.

Stability at 50 and 100% RH

A 150 mg sample of each form was placed in a closed vessel containing either pure water (RH = 100%) or a saturated solution of $Ca(NO_3)_2$ (RH = 50%), in such a way that the powder and the liquid phase were not in contact.

Grinding and kneading experiments

A 150 mg sample of gabapentin of each form was manually ground for 15 min and the X-ray powder diffraction was collected. In the cases of kneading, a drop of solvent (corresponding to a few μL) was added to 150 mg of Form II and the powder manually ground for 10 min. The powders were characterized by X-ray powder diffraction. The solvents used for the kneading experiments were acetonitrile, chloroform, DMSO, methanol, water, hexane and ethyl acetate.

Dehydration experiments

A 150 mg sample of Form I was placed in a desiccator filled with silica gel for 1 week. X-Ray powder diffraction confirmed the conversion of Form I to a mixture of Forms III and IV.

A 150 mg sample of Form I was placed in a flask and heated at 50 °C for 3 d. The diffractogram collected was characteristic of Form III.

A 150 mg sample of Form I was placed in a flask and heated at 100 °C under vacuum for 2 h. The diffractogram collected was characteristic of a mixture of Forms II, III and IV.

A 150 mg sample of Form I was used for variable temperature X-ray powder diffraction; the diffractograms were collected at 25, 60 and 100 °C. At 100 °C, complete conversion into a mixture of Forms III and IV was observed.

Reaction with hydrochloric acid

A 150 mg sample of gabapentin Form II was placed in a closed vessel containing a 6 M aqueous solution of hydrochloric acid, in such a way that the powder and the solution were not in contact. The powder was recovered after 5 d; the X-ray powder diffraction pattern confirmed complete conversion to gabapentin hydrochloride hemihydrate.

Synthesis and crystallization of gabapentin-lactam:benzoic acid co-crystals

A solution of benzoic acid (0.599 g, 4.905 mmol) and gabapentin Form II (0.5941 g, 3.469 mmol) in a mixture of ethanol (3 mL) and water (2 mL) was heated at 100 °C for 30 min. The final pH of this solution was around 5, and it was then lowered to pH 3.5 by adding a few drops of 37% HCl. This solution was left to crystallize at room temperature by slow evaporation. After 24 h colourless crystals had formed, and two different types could be distinguished: needles (benzoic acid) and prisms (co-crystal).

Crystal structure determination

Crystal data for the gabapentin-lactam:benzoic acid co-crystals were collected at 150 K on a Bruker AXS-KAPPA APEX II diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71069 Å). The X-ray generator was operated at 50 kV and 30 mA. X-Ray data collection was monitored by the SMART program (Bruker, 2003). All the data were corrected for Lorentzian, polarization and absorption effects using the SAINT and SADABS programs (Bruker, 2003). $C_{16}H_{21}NO_3$, M = 275.34, monoclinic, $P2_1/n$, a = 6.5410(4), b = 19.2190(5), c = 12.0700(6) Å, β = 97.601(7), V = 1504.01(12) Å^3, Z = 4, D_c = 1.216 g cm^{-3}, R_1 (wR_2) = 0.0449 (0.1029) for 3026 observed independent reflections (R_{int} = 0.0505). SIR97[34] was used for structure solution and full matrix least-squares refinement on F^2. All non-hydrogen atoms were refined anisotropically. H_{NH} atoms were located from a difference Fourier map, and their positional coordinates and isotropic parameters were refined. H_{CH} atoms were added in calculated positions and refined riding on their C atoms. ORTEP[35] was used for generating molecular representations, and MERCURY[36] was used both for producing packing diagrams and calculating hydrogen bonds.‡

X-Ray powder diffraction

Powder data were collected with a Panalytical X'Pert Pro instrument with an X'Celerator detector equipped with an Anton Paar TTK 450 low temperature camera. A Cu anode was used as an X-ray source at 40 kV and 40 mA. The program PowderCell 2.2[37] was used for calculating the X-ray powder patterns.

DSC measurements

Calorimetric measurements were performed in Bologna using a Perkin-Elmer Diamond equipped with a model ULSP90 intracooler. Temperature and enthalpy calibrations were performed by using high purity standards (n-decane, benzene and indium). Samples (3–5 mg) were placed in aluminium open pans. Heating was carried out at 5 °C min^{-1} in the temperature range 25 to 160 °C.

DSC data were collected in Lisbon using a Setaram DSC121 device. Samples (5–8 mg) were placed into aluminium sealed pans. Heating was undertaken at 5 °C min^{-1} between 20 and 180 °C.

Melting point apparatus

The decomposition point was observed using a Buchi B-540 instrument at a rate of 2 K min^{-1}.

Hot-stage microscopy

Hot-stage experiments were carried out using a Linkam TP94 device connected to a Linkam LTS350 platinum plate. Images were collected using the imaging software Cell from an Olympus SZX10 stereomicroscope.

Acknowledgements

This work was supported by MiUR (PRIN2006) and the University of Bologna. The Project POCI/QUI/58791/2004 and Fundação para a Ciência e Tecnologia (PhD grant SFRH/BD/40474/2007) are acknowledged.

References

1 A. A. Jensen, J. Mosbacher and S. Elg, *Mol. Pharmacol.*, 2002, **61**, 1377.
2 C. P. Taylor, *Neurology*, 1994, **44**, 510.
3 K. G. Sutton and T. P. Snutch, *Drug Dev. Res.*, 2002, **54**, 167.
4 C. P. Taylor, N. S. Gee, T.-Z. Su, J. D. Kocsis, D. F. Welty, J. P. Brown, D. J. Doodley, P. Boden and L. Singh, *Epilepsy Res.*, 1998, **29**, 233.
5 A. C. Errington, T. Stöhr and G. Lees, *Curr. Top. Med. Chem.*, 2005, **5**, 15.
6 A. B. Ettinger and C. E. Argoff, *Neurotherapeutics*, 2007, **4**, 75.
7 A. S. Kato and D. S. Bredt, *Curr. Opin. Drug Discovery Dev.*, 2007, **10**, 565.
8 E. Eisenberg, Y. River, A. Shifrin and N. Krivory, *Drugs*, 2007, **67**, 1265.
9 P. G. Vasudev, N. Shamala, K. Ananda and P. Balaram, *Angew. Chem., Int. Ed.*, 2005, **44**, 5052.
10 K. Ananda, S. Aravinda, P. G. Vasudev, K. M. P. Raja, H. Sivaramakrishnan, K. Nagarajan, N. Shamala and P. Balaram, *Curr. Sci.*, 2003, **85**, 1002.
11 J. S. Bryans, N. E. A. Chessum, N. Huther, A. F. Parsons and F. Ghelfi, *Tetrahedron*, 2003, **59**, 6221.
12 C. V. Hiremath, D. C. Hiremath and S. T. Nandibewoor, *J. Mol. Catal. A: Chem.*, 2007, **269**, 246.
13 J. A. Ibers, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 2001, **57**, 641.
14 D. E. Butler and B. J. Greenman, *US Pat.*, 4 894 476, 1990.
15 H. A. Reece and D. C. Levendis, *Acta Crystallogr., Sect. C*, 2008, **64**, o105.
16 Y. Kumar, C. Khanduri, K. K. Ganagakhedkar, R. Chakraborthy, H. N. Dorwal, A. Rohatgia and K. Panda, *Int. Pat.*, WO 2004/106281 A1, 2004.
17 J. B. Lladó, R. G. Cruz, E. M. Grau, M. Onrubia and M. Del Carmen, *US Pat.*, 6 521 787 B1, 2003.
18 L. R. Chen, S. R. Babu, C. J. Calvitt and B. Tobias, *US Pat.*, 6 800 782 B2, 2004.
19 M. Pesachovich, C. Singer and G. Pilarski, *US Pat.*, 6 255 526 B1, 2001.
20 J. Hartenstein and W. Heldt, *US Pat.*, 4 024 175, 1977.
21 *US Pat. Appl.*, 2006/02355079 A1, 2006.
22 M. Wenger and J. Bernstein, *Cryst. Growth Des.*, 2008.
23 D. Braga, F. Grepioni, L. Maini, R. Brescello and L. Cotarca, *CrystEngComm*, 2008, **10**, 469.
24 A. Cutrignelli, N. Denora, A. Lopedota, A. Trapani, V. Laquintana, A. Latrofa, G. Trapani and G. Liso, *Int. J. Pharm.*, 2007, **332**, 98.

25 A. S. Kearney, S. C. Mehta and G. W. Radebaugh, *Int. J. Pharm.*, 1992, **78**, 25.
26 D. Braga, L. Maini, M. Mazzotti, K. Rubini and F. Grepioni, *CrystEngComm*, 2003, **5**, 154.
27 D. Braga, M. Cadoni, F. Grepioni, L. Maini and K. Rubini, *CrystEngComm*, 2006, **8**, 756.
28 D. Braga, L. Maini, M. Mazzotti, K. Rubini, A. Masic, R. Gobetto and F. Grepioni, *Chem. Commun.*, 2002, 2296.
29 D. Braga, G. Cojazzi, D. Emiliani, L. Maini and F. Grepioni, *Chem. Commun.*, 2001, 2272.
30 D. Giron, M. Mutz and S. Garnier, *J. Therm. Anal. Calorim.*, 2004, **77**, 709.
31 F. Henle, J. Leemhuis, C. Fischer, H. H. Bock, K. Lindemeyer, T. J. Feuerstein and D. K. Meyer, *J. Pharmacol. Exp. Ther.*, 2006, **319**, 181.
32 T. Jehle, W. A. Lagreze, E. Blauth, R. Knorle, P. Schnierle, C. H. Lucking and T. J. Feuerstein, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 2000, **362**, 74.
33 H. Potschka, T. J. Feuerstein and W. Loscher, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, 2000, **361**, 200.
34 A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori and R. Spagna, *J. Appl. Crystallogr.*, 1999, **32**, 115.
35 L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565.
36 C. F. Macrae, P. R. Edgington, P. McCabe, E. Pidcock, G. P. Shields, R. Taylor, M. Towler and J. van De Streek, *J. Appl. Crystallogr.*, 2006, **39**, 453.
37 W. Kraus and G. Nolze, *Powder Cell*, version 2.2, Federal Institute for Material Research and Testing, Berlin, Germany, 1999.