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International Journal of Pharmaceutics 327 (2006) 51–57
INTERNATIONAL JOURNAL OF PHARMACEUTICS
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Effect of pressure up to 5.5 GPa on dry powder samples of chlorpropamide form-A

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Received 2 May 2006; received in revised form 11 July 2006; accepted 12 July 2006
Available online 16 July 2006

Abstract

The effect of pressure up to 5.5 GPa on a dry powder sample of chlorpropamide (4-chloro-*N*-((propylamino)-carbonyl)-benzenesulfonamide), form-A (sp. gr. $P2_12_12_1$, $a = 9.066$ Å, $b = 5.218$ Å, $c = 26.604$ Å), was studied *in situ* in a Merrill–Bassett diamond anvil cell using high-resolution X-ray powder diffraction (a synchrotron radiation source at SNBL ESRF, Grenoble). No evidence of the polymorphic transformation of chlorpropamide form-A to form-C was observed. The A–C polymorphic transition on tabletting previously reported by Otsuka et al. (1989) is therefore likely to be due to local heating effects. Similarly, the phase transitions of form-A reported by Cao (2002) to be induced by pressure applied to a sample in its saturated ethanol solution (at 0.9 and at 2.0 GPa) would appear to be solvent-mediated. In the dry sample, a phase transition may be supposed to occur at pressures above 4 GPa, but this requires further studies.

Keywords: Pressure; Polymorphism; Polymorphic transformation; X-ray powder diffraction; Chlorpropamide

1. Introduction

The problem of polymorphic transitions in drug substances is important for several reasons. If a polymorphic transition occurs during manufacturing process, the uncontrolled formation of another polymorph as compared to the starting material can result in the deterioration of the quality of a dosage form in terms of its bioavailability, or shelf-life. It can also have consequences if a patent specifies the manufacture and sale of a particular polymorph. On the other hand, an ability to control the polymorphism of a drug opens new routes to improving the quality of an already known product and to launching new products into the market (Brittain, 1999; Bernstein, 2002).

The possibility of inducing polymorphic transitions in drug substances during tabletting has attracted attention for a rather long time and has been reported in the literature for several compounds (Nogami et al., 1969; Chan and Doelker, 1985; Boldyreva and Boldyrev, 1999; Brittain, 1999; Bernstein, 2002). Typically, in such studies a sample (a dry powder or a slurry in a solvent) was compressed and then characterized *a posteriory*, mainly using X-ray powder diffraction. Polymorphic transitions observed in such experiments could result from local pressure increase, but also from shear strain, and local heating. Polymorphic transitions on tabletting are not necessarily of a "crystalline solid to crystalline solid" type, but can proceed via amorphisation, melting and/or recrystallization. Model experiments have shown, that the temperature of the sample during tabletting can influence polymorphic transitions induced in the sample (Otsuka et al., 1989, 1995; Matsumoto et al., 1991; Boldyreva and Boldyrev, 1999). Model experiments on samples in a hydrostatic medium have also shown, that pure hydrostatic compression can have an opposite effect as compared to shear stresses. For example, grinding induces a polymorphic transformation of paracetamol-II into paracetamol-I, whereas a reverse transformation occurs on applying hydrostatic pressure (Boldyreva et al., 2002). When conducting experiments under hydrostatic conditions, one excludes the effects of shear stresses and of local heating, but another important possibility must be controlled,

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doi:10.1016/j.ijpharm.2006.07.019

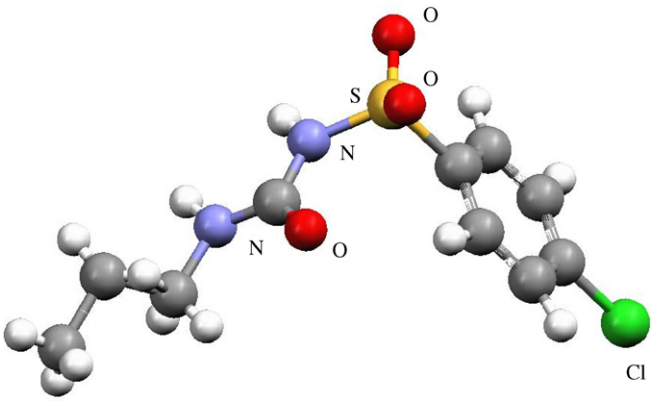

Fig. 1. A molecule of chlorpropamide (4-chloro-*N*-((propylamino)-carbonyl)-benzenesulfonamide), form-A.

namely, the solvent-mediated effects due to the possible interaction between the solid sample and the pressure-transmitting medium. No polymorphic transition could be induced by pressure in a Co(III)-coordination compound in a fluorinated oil, but it was observed easily at a relatively low pressure in alcohol (Boldyreva et al., 2000a). Examples are described, when the effects of tabletting on a solid drug substance were also solvent-mediated. Thus, no phase transitions were observed on tabletting dry intact powder of indomethacin, but occurred if an ethanol slurry was compressed (Okumura et al., 2006). One should be especially careful, if the solid is soluble in the pressure-transmitting liquid at ambient conditions. The crystallization of new polymorphs and solvates of drug substances at high hydrostatic pressures has also been described in several recent publications (Fabbiani et al., 2003, 2004, 2005a,b). Different solvents gave different high-pressure phases/solvates.

Chlorpropamide ((4-chloro-*N*-((propylamino)-carbonyl)-benzenesulfonamide), Fig. 1) is a member of the sulphonylurea group of compounds, and is widely used as an oral antidiabetic agent (Physician's Desk Reference, 2003). Seven chlorpropamide polymorphs and a benzene solvate have been reported in the literature (Simmons et al., 1973; Burger, 1975; Al-Saieq and Riley, 1982; De Villiers and Wurster, 1999; Vemavarapu et al., 2002), but the crystal structure has been solved for only one polymorph, sp. gr. $P2_12_12_1$, $a = 9.066$ Å, $b = 5.218$ Å, $c = 26.604$ Å (Koo et al., 1980), most commonly termed "form-A" (Simmons et al., 1973; Otsuka et al., 1989, 1995; Matsumoto et al., 1991), more rarely termed form-III (Burger, 1975), or form-IV (Al-Saieq and Riley, 1982). This form is the commercially manufactured one, and it is considered to be the thermodynamically stable form at ambient conditions (Simmons et al., 1973; Burger, 1975; Al-Saieq and Riley, 1982). For other forms, even the cell parameters remain unknown, but the powder diffraction patterns differ so noticeably, that a pattern can characterize a form unambiguously. The structures of the different forms remaining unknown, powder diffraction patterns are used even to calculate the relative content of the forms in a mixture (De Villiers and Wurster, 1999).

Chlorpropamide can be considered as a model compound to study polymorphic transformations on tabletting (Otsuka et al., 1989, 1995; Matsumoto et al., 1991). On tabletting, form-A has been reported to transform partially into another polymorph, form-C (Otsuka et al., 1989, 1995; Matsumoto et al., 1991; Koivisto and Lehto, 2006). The density of the form-A (measured using an air comparison pycnometer) is larger, than the density of the form-C (measured in the same way), and this let Otsuka et al. conclude, that pressure increase on tabletting cannot account for the A–C transformation (Otsuka et al., 1989; Matsumoto et al., 1991). Form-C is known to be formed from any other form of chlorpropamide on heating up to about 115 °C (Simmons et al., 1973; Burger, 1975; Al-Saieq and Riley, 1982), and one might suppose the reported form-A to form-C transformation on tabletting could be a result of local heating, melting and/or recrystallization (Otsuka et al., 1989, 1995; Matsumoto et al., 1991).

In a model study of the effect of hydrostatic pressure on form-A of chlorpropamide by Raman spectroscopy in a diamond anvil cell *in situ*, no "A-to-C" transformation with increasing pressure was observed, but two polymorphic transformations were claimed to occur at approximately 0.9 and 2.0 GPa (Cao, 2002). Since the saturated solution of chlorpropamide in ethanol was used as a pressure-transmitting liquid in these experiments, one cannot exclude the role of ethanol in these transformations.

In this work, we decided to test, if any pressure-induced transformations can be induced by compressing a *dry* powder sample of chlorpropamide form-A to high pressures in a diamond anvil cell, and monitoring the polymorphic form *in situ* by high-resolution powder X-ray diffraction. In the absence of a pressure-transmitting liquid, compression of a powder sample in a DAC becomes non-homogeneous throughout the sample, resulting in the broadening of the X-ray diffraction peaks. However, this does not prevent one from refining cell parameters (although at a lower precision), and from checking, if a polymorphic transition occurs.

This is the first paper in a series documenting a systematic study of the effect of pressure on chlorpropamide crystals, using different starting polymorphs and pressure-transmitting liquids (if any). As was demonstrated recently (Murli et al., 2003; Boldyreva et al., 2005; Goryainov et al., 2005, 2006), by varying starting polymorphs, one can obtain different high-pressure forms at the same *P–T* conditions using the same pressure-transmitting liquid.

2. Materials and methods

Chlorpropamide form-A (batch # 31H0722) was obtained from Sigma Chemical Co. (St. Loius, MO, USA) and used as received. An X-ray powder diffraction test has shown, that the sample contained only pure form-A, at least within the accuracy of the technique (Fig. 2a).

Quasihydrostatic pressure was created in a modified Merrill–Bassett four-screw diamond anvil cell (DAC) with 0.6 mm diameter culets (Ahsbahs, 1995). A hole (0.2 mm diameter) in a stainless steel gasket was filled manually as densely as possible with a powder sample. Compression was achieved by tightening the screws of the DAC, and pressure was controled

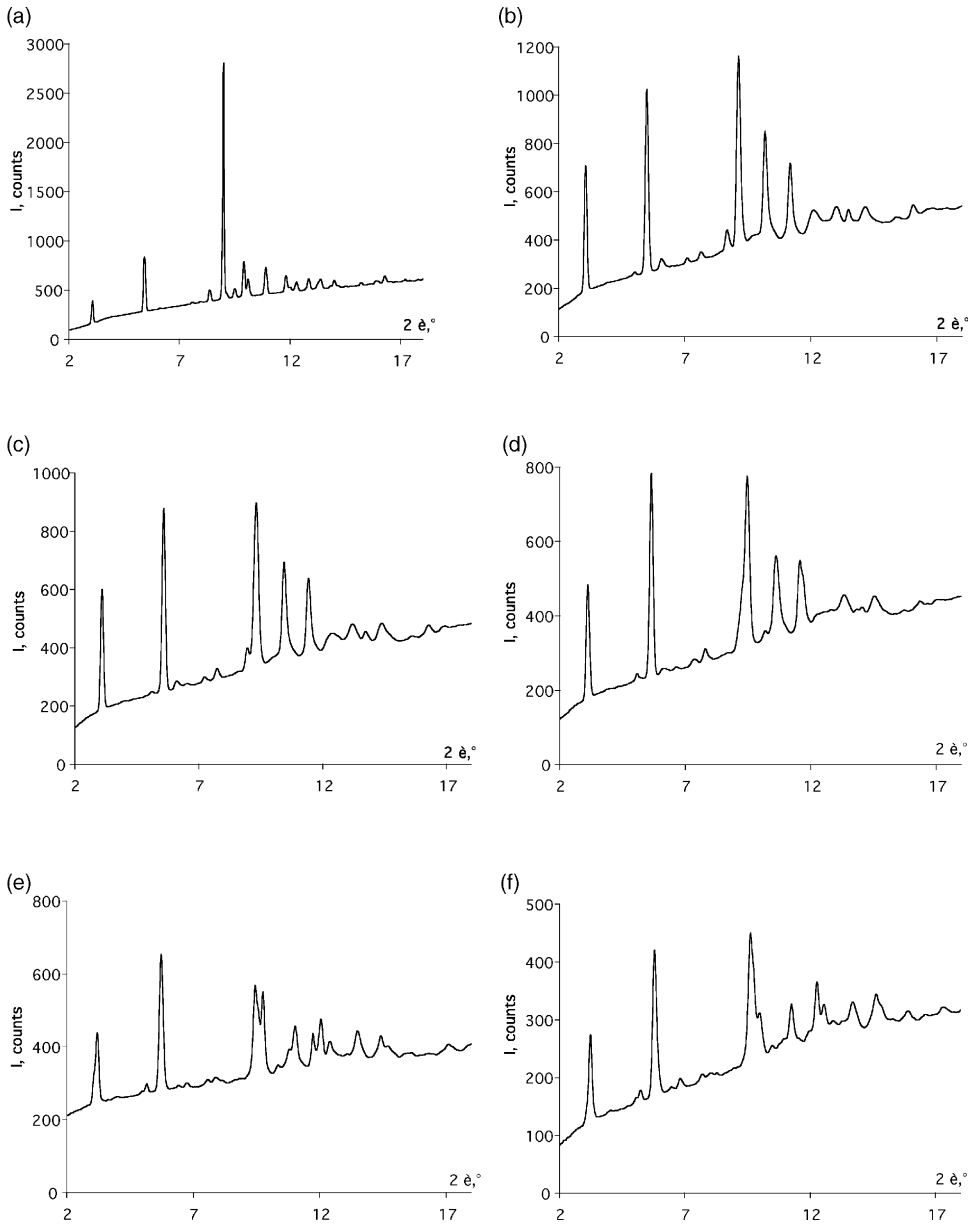

Fig. 2. Powder diffraction patterns of chlorpropamide: a: ambient pressure; b: 0.6 GPa; c: 1.3 GPa; d: 2 GPa; e: 3.7 GPa; f: 5.5 GPa.

by a line shift in Ruby fluorescence (Piermarini et al., 1975). During the experiments, the DAC was kept at constant ambient temperature. The packing density of the powder in the cell was not measured, but it obviously increased after applying pressure, as indicated by a shrinkage in the gasket hole with increasing pressure in the course of the experiment.

The effect of pressure on the crystal structure of chlorpropamide form-A was followed using an angular-dispersive X-ray powder diffraction technique in transmission mode with a monochromatized synchrotron radiation source at the Swiss-Norwegian Beam Lines (BM1A) at ESRF ($\lambda = 0.71085$ Å, collimator width and height 0.15 mm). Diffraction patterns were registered with a MAR345 image plate detector (pixel size 0.12 mm, 2300 × 2300 pixels in image). The frames were measured with exposing time equal to 900–3600 s, with oscillation in $\phi \pm 3°$. The distance from crystal to detector, the beam center position, the tilt angle and the tilt plane rotation angle were refined using a Si standard put at a diamond anvil of the open DAC in a special calibration experiment.

ULM (Brueggemann et al., 1992) was used for the refinement of cell parameters. Fragments of crystal structure were plotted using Mercury (Bruno et al., 2002).

3. Results and discussion

Typical macroscopic pressures recorded during the tableting of pharmaceutical materials are in the range 100–400 MPa, although local pressures within a tablet may be considerably higher than this. Powder diffraction patterns collected for chlorpropamide form-A at several pressures up to 5.5 GPa are pre-

sented in Fig. 2. Since no pressure-transmitting liquid was used, the pressure was not ideally homogeneous, and noticeable broadening of the peaks could be observed, especially at higher pressures. The intensity ratio indicated at the preferred orientation of particles in the sample, typical for powder samples pressed in a DAC. There was no evidence of a polymorphic transformation of form-A into form-C with increasing pressure. The changes in the powder diffraction patterns can be interpreted in terms of the anisotropic compression of form-A: all the patterns could be indexed as the original form-A, and the values of cell parameters and volume could be refined at different pressures (Fig. 3). At about 4 GPa, a shoulder appeared at the low angle reflection (0 0 2), which became less pronounced again at a higher-pressure 5.5 GPa (Fig. 2e and f). This can be a consequence of non-hydrostatic conditions, but may indicate also at some structural change (in any case, not at the A–C transformation) at this pressure value. Small deviations from smooth $V(P)$, $b(P)$, and $c(P)$ curves (Fig. 3), and a kink at the $\Delta b/b(P)$ dependence (Fig. 6) may serve as other possible indications at a pronounced structural change at about 4 GPa. At the same time, they can also result from a deterioration of the quality of the diffraction patterns due to peak broadening at higher pressures. This requires further study. In any case, it can be deduced from our data that the polymorphic transformation of chlorpropamide form-A to form-C on tabletting that has been previously reported (Otsuka et al., 1989, 1995; Matsumoto et al., 1991) is most likely to be due to local heating effects. Likewise, the pressure-induced phase transitions at 0.9 and 2.0 GPa detected by Raman spectroscopy on a sample of chlorpropamide form-A in its saturated ethanol solution by Cao (2002) would seem to be most likely solvent-mediated.

Chlorpropamide form-A crystals turned out to be much more compressible, than other previously studied drug substances, such as the polymorphs of paracetamol (Boldyreva et al., 2000b, 2002) (Fig. 4). This high compressibility can be correlated both with the conformational flexibility of chlorpropamide molecules (Fig. 1) and with the molecular packing in the crystal structure. Chlorpropamide form-A has pleated bands of hydrogen-bonded molecules with alternating hydrophobic and hydrophilic regions (Fig. 5a and b) (Koo et al., 1980). The pleated bands in chlorpropamide form-A show some similarity with the pleated layers in paracetamol-I (Fig. 5c). Fig. 6 illustrates the anisotropy of structural strain in chlorpropamide form-A crystals compared to that in paracetamol forms I and II (Boldyreva et al., 2000b, 2002). Chlorpropamide form-A crystals are noticeably more compressible in the direction normal to the pleated bands (*b*-direction). Relative linear strain in this direction is comparable with linear strain in the direction normal to pleated layers in paracetamol-I (also *b*-direction), and with compression normal to flat layers in paracetamol-II, up to about 4 GPa, and becomes larger at higher pressures. Linear strain in the planes normal to *b*-direction in chlorpropamide is practically isotropic, although crystal structure is orthorhombic. A similar effect was observed previously for orthorhombic paracetamol-II (Boldyreva et al., 2002). The value of linear strain in these planes is comparable

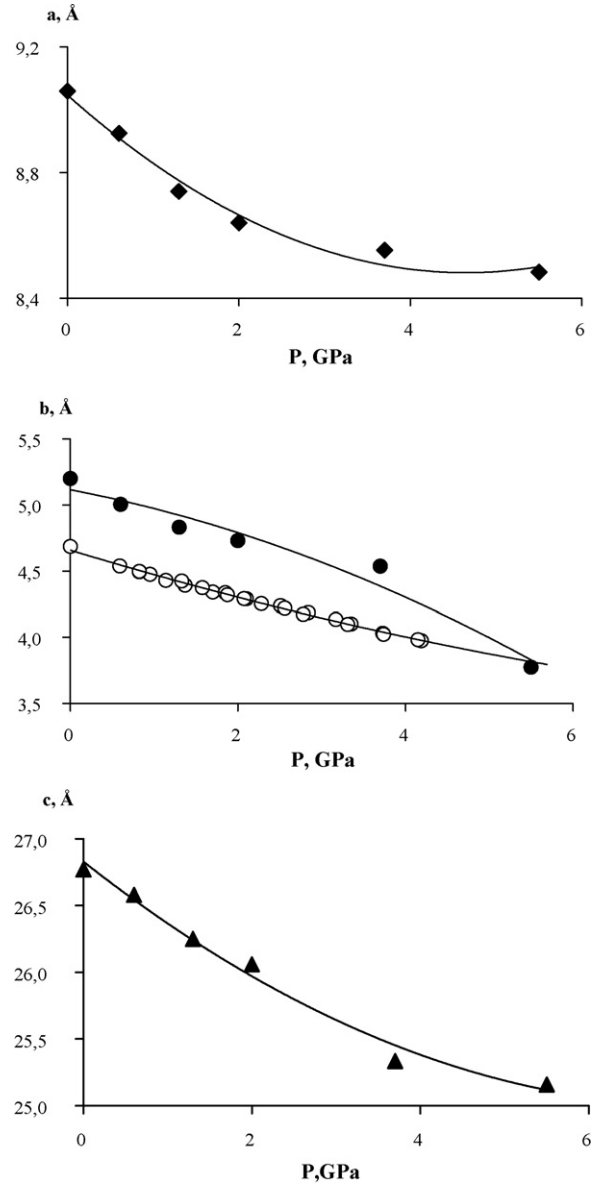

Fig. 3. Changes in cell parameters of chlorpropamide vs. pressure; a: parameter *a*; b: parameter *b* in chlorpropamide (black symbols) and *b*/2 in paracetamol-I (open symbols); c: parameter *c*.

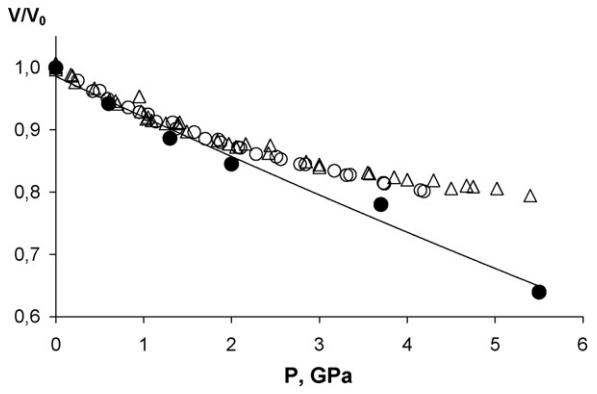

Fig. 4. Relative volume change with increasing pressure in chlorpropamide (this study; solid symbols) as compared with paracetamol-I (Boldyreva et al., 2000b) and paracetamol-II (Boldyreva et al., 2002) (open symbols).

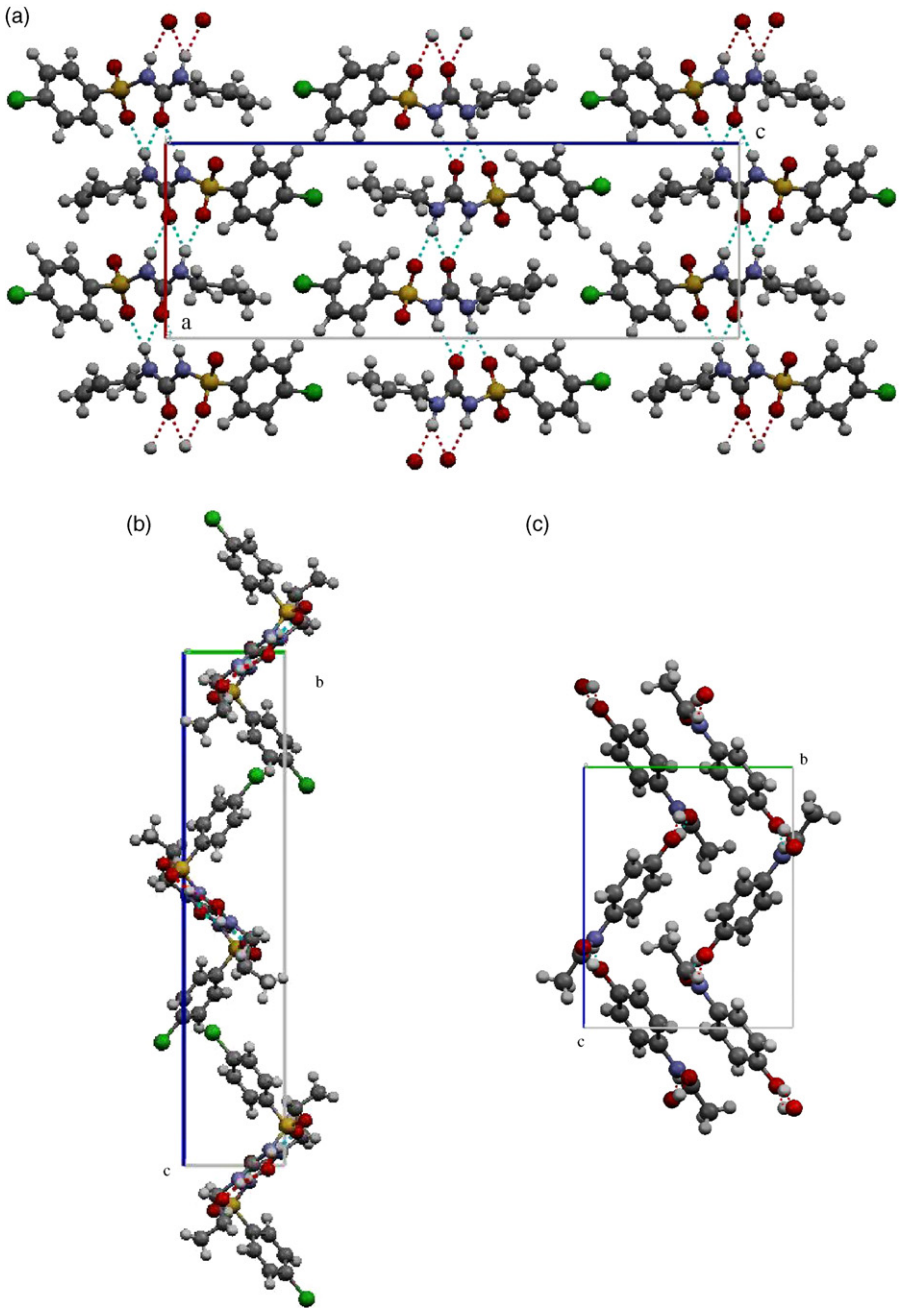

Fig. 5. Fragments of the crystal structure of chlorpropamide form-A in different orientations (a and b) and, for a comparison, of paracetamol-I (c). In electronic colour version: red, oxygen; blue, nitrogen; grey, carbon; yellow, sulfur; green, chlorine; small white circles: hydrogen. The plots were prepared using Mercury (Bruno et al., 2002).

with that in the flat hydrogen-bonded layers in paracetamol-II (Boldyreva et al., 2002) and with an average between the expansion and the compression in different directions within the pleated layers in paracetamol-I (Boldyreva et al., 2000b). At about 5.5 GPa the distance between the pleated bands in chlorpropamide form-A (the value of *b* parameter) becomes equal to the distance between the pleated layers in paracetamol-I (the value *b*/2) at the same pressure (Fig. 3b). Thus, the anisotropic response to applied stress is consistent with the known arrangement of molecules in the unit cell and may reflect the anisotropy of intermolecular interactions in chlorpropamide form-A crystals. The similarity of the values of linear strain measured in selected crystallographic directions in chlorpropamide, form-A (dry powder), in paracetamol-I (single crystals or powders in various liquids), and in paracetamol-II (powder in various liquids) suggest, that the non-hydrostatic conditions do not have a significant effect on the anisotropic response of the molecules in a crystal, and the measured anisotropy of lattice strain is to a large extent determined by the anisotropy of crystal structure, even if pressure in the sample is non-homogeneous.

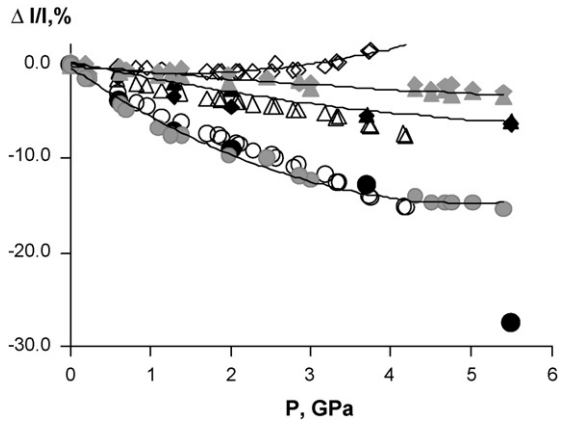

Fig. 6. Linear strain in directions of the principal axes of strain tensor of chlorpropamide (black symbols, rhombs: along *a*; triangles: along *c*; circles: along *b* crystallographic directions). For a comparison, the corresponding values for the monoclinic paracetamol-I (white symbols) and for the orthorhombic paracetamol-II (grey symbols) are plotted.

4. Conclusion

The most important result of the present study is that obviously no A–C polymorphic transformation could be observed, when pressure was applied to a dry powder sample of chlorpropamide form-A. A polymorphic transformation of chlorpropamide form-A to form-C that was reported during tabletting (Otsuka et al., 1989, 1995; Matsumoto et al., 1991) must therefore be due to local heating effects. If no polymorphic transformations are observed under conditions of non-homogeneous pressure, the probability that they can be induced under ideally hydrostatic conditions is very low. Much more often, even the polymorphic transitions that occur under non-hydrostatic conditions do not take place on hydrostatic compression (see e.g. Boldyreva et al., 2002). The pressure-induced phase transitions at 0.9 and 2.0 GPa studied by Raman spectroscopy on a sample of chlorpropamide form-A in its saturated ethanol solution (Cao, 2002) appear to be solvent-mediated. In the dry sample, a phase transition may be supposed to occur at pressures above 4 GPa, but this requires further studies. A detailed study of the effect of pressure on different starting polymorphs of chlorpropamide in various liquids is in progress. It will help us to understand better the nature of the pressure-induced polymorphic transitions in this system, and is very promising for identifying new chlorpropamide high-pressure forms, that might be preserved on decompression.

Acknowledgements

The study was supported partly by RFBR (grant 05-03-32468), by Award NO-008-X1 of the BRHE program (CRDF and Russian Ministry of Education) and by Multidisciplinary Integration Projects (#49 and #110) of SB RAS. Experimental assistance by the staff of the Swiss-Norwegian Beamlines at ESRF is gratefully acknowledged. Peter Wildfong is thanked for providing the chlorpropamide sample, and Dr. Evgenyi Shalaev—for his contributions to this collaborative research project.

References

Ahsbahs, H., 1995. 20 Jahre Merrill–Bassett–Zelle. Einige Neuheiten. Z. Kristallogr. Suppl. 9, 42.

Al-Saieq, S.S., Riley, G.S., 1982. Polymorphism in sulphonylurea hypoglycaemic agents: II. Chlorpropamide. Pharm. Acta Helv. 57, 8–11.

Bernstein, J., 2002. Polymorphism in molecular crystals. In: IUCr Monographs on Crystallography. Clarendon Press, Oxford.

Boldyreva, E.V., Boldyrev, V.V. (Eds.), 1999. Reactivity of Molecular Solids, Molecular Solid State Series, vol. 3. Wiley and Sons.

Boldyreva, E.V., Ahsbahs, H., Uchtmann, H., Kascheeva, N.E., 2000a. Effects of pressure on the two polymorphs of $[Co(NH_3)_5NO_2]I_2$: the anisotropy of lattice distortion and a phase transition. High Press. Res. 17, 79–99.

Boldyreva, E.V., Shakhtshneider, T.P., Vasilchenko, M.A., Ahsbahs, H., Uchtmann, H., 2000b. Anisotropic crystal structure distortion of the monoclinic polymorph of acetaminophen at high hydrostatic pressures. Acta Crystallogr. B 56, 299–309.

Boldyreva, E.V., Shakhtshneider, T.P., Ahsbahs, H., 2002. Effect of high pressure on the polymorphs of paracetamol. J. Therm. Anal. Calorim. 68, 437–452.

Boldyreva, E.V., Ivashevskaya, S.N., Sowa, H., Ahsbahs, H., Weber, H.-P., 2005. Effect of hydrostatic pressure on the γ-polymorph of glycine 1. A polymorphic transition into a new δ-form. Z. Kristallogr. 220, 50–57.

Brittain, H.G. (Ed.), 1999. Polymorphism in Pharmaceutical Solids. Drugs and the Pharmaceutical Sciences Series, vol. 95. Marcel Dekker.

Brueggemann, R., Mueller, B., Debaerdemaeker, T., Schmid, G., Thewalt, U., 1992. Computing Program ULM for X-ray Crystallography. University of Ulm, Germany.

Bruno, I.J., Cole, J.C., Edgington, P.R., Kessler, M., Macrae, C.F., McCabe, P., Pearson, J., Taylor, R., 2002. New software for searching the Cambridge structural database and visualizing crystal structures. Acta Crystallogr. B 58, 389–397.

Burger, A., 1975. Zur Polymorphie oraler Antidiabetika. Sci. Pharm. 43, 152–161.

Cao, W., 2002. Polymorphic Transformations under Compression. Thesis, Purdue University.

Chan, H.K., Doelker, E., 1985. Polymorphic transformation of some drugs under compression. Drug Dev. Ind. Pharm. 11, 315–332.

De Villiers, M.M., Wurster, D.E., 1999. Isothermal interconcersion of chlorpropamide polymorphs kinetically quantified by XRPD, diffuse reflectance FTIR, and isoperibol solution calorimetry. Acta Pharm. 49, 79–88.

Fabbiani, F., Allan, D.R., Dawson, A., David, W.I.F., McGregor, P.A., Oswald, I.D.H., Parsons, S., Pulham, C.R., 2003. Pressure-induced formation of a solvate of paracetamol. Chem. Commun., 3004–3005.

Fabbiani, F.P.A., Allan, D.R., David, W.I.F., Moggach, S.A., Parsons, S., Pulham, C.R., 2004. High-pressure recrystallization—a route to new polymorphs and solvates. Cryst. Eng. Commun. 6, 504–511.

Fabbiani, F.P.A., Allan, D.R., Marshall, W.G., Parsons, S., Pulham, C.R., Smith, R.I., 2005a. High-pressure recrystallization—a route to new polymorphs and solvates of acetamide and parabanic acid. J. Crystal Growth 275, 185–192.

Fabbiani, F.P.A., Allan, D.R., Parsons, S., Pulham, C.R., 2005b. An exploration of the polymorphism of piracetam using high pressure. Cryst. Eng. Commun. 7, 179–186.

Goryainov, S.V., Kolesnik, E.N., Boldyreva, E.V., 2005. A reversible pressure-induced phase transition in β-glycine at 0.76 GPa. Phys. B Condens. Matter 357, 340–347.

Goryainov, S.V., Boldyreva, E.V., Kolesnik, E.N., 2006. Raman observation of a new (ζ) polymorph of glycine? Chem. Phys. Lett. 419, 496–500.

Koivisto, M., Lehto, V.-P., 2006. Grazing incidence X-ray diffraction studies of pharmaceutical tablets. In: Polymorfi, Fysikaalisen farmasian XVII vuosittainen symposium: Vesi farmasiassa, p. 28 (Abstracts).

Koo, C.H., Cho, S.I., Yeon, Y.H., 1980. The crystal and molecular structure of chlorpropamide. Arch. Pharmacol. Res. 3, 37–49.

Matsumoto, T., Kaneniwa, N., Higuchi, S., Otsuka, M., 1991. Effects of temperature and pressure during compression on polymorphic transformation and crushing strength of chlorpropamide tablets. J. Pharm. Pharmacol. 43, 74–78.

Murli, C., Sharma, S.M., Karmakar, S., Sikka, S.K., 2003. α-Glycine at high pressures: a Raman scattering study. Physica B 339, 23–30.

Nogami, H., Nagai, T., Fukuoka, E., Yotsuyanagi, T., 1969. Dissolution kinetics of barbital polymorphs. Chem. Pharm. Bull. 17, 23–31.

Okumura, T., Ishida, M., Takayama, K., Otsuka, M., 2006. Polymorphic transformation of indomethacin under high pressures. J. Pharm. Sci. 95, 689–700.

Otsuka, M., Matsumoto, T., Kaneniwa, N., 1989. Effects of the mechanical energy of multi-tableting compression on the polymorphic transformations of chlorpropamide. J. Pharm. Pharmacol. 41, 665–669.

Otsuka, M., Matsumoto, T., Higuchi, S., Otsuka, K., Kaneniwa, N., 1995. Effect of compression temperature on the consolidation mechanism of chlorpropamide polymorphs. J. Pharm. Sci. 84, 614–618.

2003. Physician's Desk Reference. Thomson Publishing, Montvale, NJ, USA.

Piermarini, G.J., Block, S., Barnett, J.D., Forman, R.A., 1975. Calibration of the pressure dependence of the R1 ruby fluorescence line to 195 kbar. J. Appl. Phys. 46, 2774–2780.

Simmons, D.L., Ranz, R.J., Gyanchandani, 1973. Polymorphism in pharmaceuticals III chlorpropamide. Can. J. Pharm. Sci. 8, 125–127.

Vemavarapu, C., Mollan, M.J., Needham, T.E., 2002. Crystal doping aided by rapid expansion of supercritical solutions. AAPS PharmSciTech. 3 (article 29) http://www.aapspharmsci.org.