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Polymorphism of azlocillin sodium

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Abstract

The polymorphism of azlocillin sodium (AZ) has not been discussed sufficiently in the literature. The results of infrared (IR) spectroscopy, thermal analysis (combined thermogravimetry TG and differential analysis DTA), and scanning electron microscopy (SEM) confirm that recrystallization of lyophilized azlocillin sodium from simple solvent acetonitrile causes polymorphic transformation. The new polymorph obtained by us has a crystalline form.

Keywords: Azlocillin sodium; β-Lactam antibiotics; Polymorphism; Recrystallization; Infrared spectroscopy; Thermogravimetry; Differential thermal analysis; Scanning electron microscopy

Nowadays, when describing the physicochemical properties of the active substance on drug registration documents pharmaceutical companies have a section on polymorphism (Borka and Haleblian, 1990).

It is well known that crystallinity is an important factor in the chemical stability of drugs (Pikal et al., 1977; Ahlneck and Zografi, 1990; Otsuka and Kaneniwa, 1990; Kalinkova and Ovcharova, 1994).

Azlocillin sodium (Abrotil, Azlin, Securopen-Bayer) was synthesized in Bayer Research Laboratories for the first time in 1971. In the most extensive reviews on the drugs, crystal polymorphism data were not published (Pikal et al., 1978; Thoma and Serno, 1984; Borka and Haleblian, 1990; Borka, 1991) about azlocillin sodium.

Pavlova et al. (1988) described crystal and non-crystal forms of AZ. These authors used different procedures — pressure-, vacuum- and spray-drying as well as storage under different relative humidity conditions (20–95%).

The results published by us on AZ (Kalinkova et al., 1988; Kalinkova et al., 1989) are in good agreement with the data reported at the same time by Pavlova et al. (1988). Indeed, perfect coincidence in the conclusions concerning the influence of relative humidity on the crystallinity of AZ was observed.

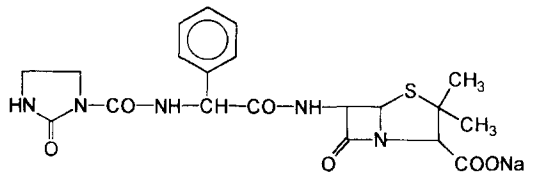

Fig. 1. Structural formula of azlocillin sodium.

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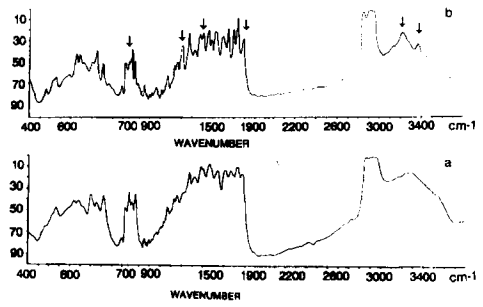

Fig. 2. IR spectra /in nujol/ of lyophilized azlocillin sodium™ (a) and azlocillin sodium recrystallized from acetonitrile (b).

The new polymorphic form of AZ prepared by us, was investigated by means of IR-spectroscopy, thermoanalysis (TG and DTA) and scanning electron microscopy (SEM). Our polymorphic form of AZ is different from Pavlova's crystal azlocillin sodium. These authors prepared crystal AZ by crystallization from aqueous solution, while we prepared the new polymorph AZ by recrystallization from acetonitrile. The comparison of IR spectral data give proof of their differences. The former, as detectable from the three bands (700, 720, 760 cm^{-1}) in the range 700–900 cm^{-1}, shows greater intensity than the latter (Pavlova et al., 1988). The opposite is observed in our spectrum (720, 750, 780 cm^{-1}). There are also slight differences in the whole spectra.

The aim of the present study was to report a new crystal polymorph of AZ. The azlocillin sodium in Fig. 1 (Batch No. 070294, a Bulgarian product meeting the requirements of US Pharmacopoeia XXI (Joint-Stock Company, Razgrad, Bulgaria)) was used as received. The solvent acetonitrile was analytical grade (Merck, Darmstadt, Germany). An appropriate amount (w/v) of AZ was suspended in acetonitrile. The crystal polymorph was obtained by slow evaporation of the solvent at room temperature.

Azlocillin sodium and its new crystal polymorph do not have a defined melting point (decomposition). The IR spectra of the polymorph AZ and of the lyophilized AZ™ in Nujol suspensions, were recorded and interpreted in detail in the region 3800–400 cm^{-1}. There were significant differences (Fig. 2) in the IR spectral characteristics (amide I, II, III, IV, V and VI, as well as in the 3600–3100 cm^{-1} range) among the lyophilized AZ™ (a) and the polymorph AZ (b).

The results obtained by our IR spectroscopic investigations are in good agreement with those published in the literature (Bellamy, 1957). This author described that the amide I band in crystalline benzylpenicillin sodium appears at about 1700 cm^{-1} while the same band in amorphous benzylpenicillin sodium was observed at approximately 1667 cm^{-1}.

The absence of an IR spectral band at approximately 2260 cm^{-1}, $\nu C{\equiv}N$; the heating behaviour of AZ-crystals (b) embedded in silicon oil, where bubbles of solvent (acetonitrile) are not generated; the lower weight loss (2.8%) by TG; and the shape of the DTA curve are all proof of the formation of a new polymorph AZ.

We used the classical method recommended by Haleblian (1975) for distinguishing polymorphs from solvates, or clathrates, respectively. The discovery that many antibiotic-antibacterials can form solvates is very important in this respect (Haleblian, 1975). Contrary to our expectations in the present study, the recrystallization of AZ (from acetonitrile) does not cause solvation but polymorphic transformation. In previ-

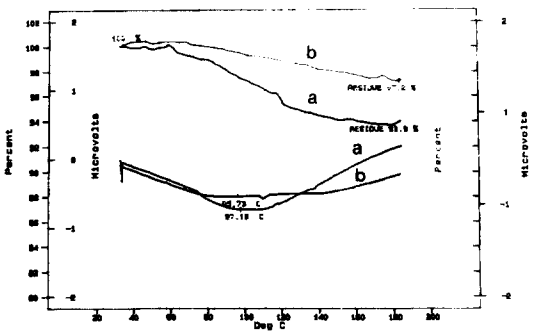

Fig. 3. TG and DTA of lyophilized azlocillin sodium™ (a) and azlocillin sodium recrystallized from acetonitrile (b).

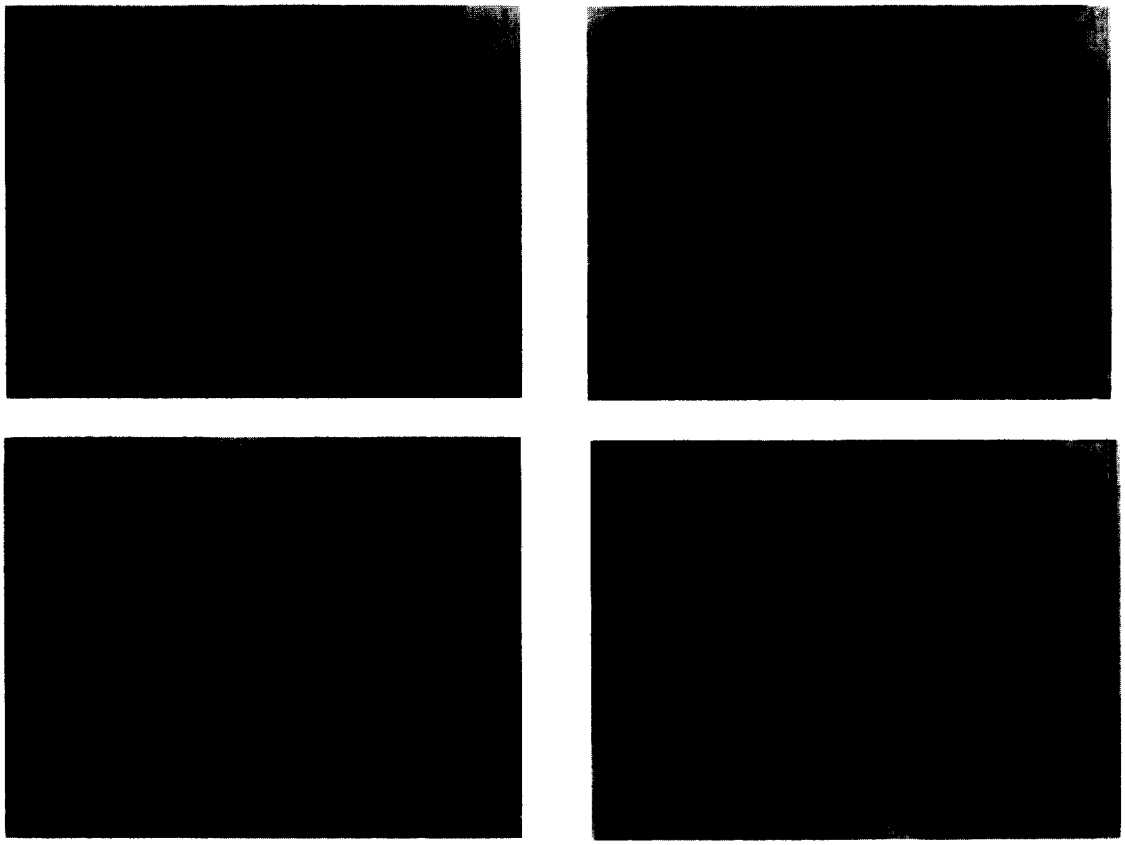

Fig. 4. Scanning electron microphotographs of lyophilized azlocillin sodium™ (a, × 500; a', × 4000, markers 100 μm) and azlocillin sodium recrystallized from acetonitrile (b, × 500; b', × 4000, markers 100 μm).

ous papers (Kalinkova et al., 1990; Kalinkova and Dimitrova, 1995), we reported the formation of the solvated and hydrate-solvated modifications of β-lactam antibiotics.

The results of TG and DTA analysis are presented in Fig. 3. The TG curves clearly show the differences in the weight loss (temperature range 30–180°C) between lyophilized AZ™ (a) and polymorph AZ (b), 6.1% and 2.8%, respectively.

The DTA curve for lyophilized AZ (a) has one endothermic maximum at 97.19°C and the DTA curve for polymorph AZ (b) has also one endothermic maximum at 95.73°C. Fig. 4 illustrates the different crystal forms of the lyophilized AZ and the polymorph AZ.

In summary, azlocillin sodium can also exist in a new crystal polymorph, which was prepared by us and proved by means of IR-spectroscopy, TG-DTA and SEM analysis.

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References

Ahlneck, C. and Zografi, G., The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state (Review). *Int. J. Pharm.*, 62 (1990) 87–95.

Bellamy, L.J., *The Infrared Spectra of Complex Molecules*, Moscow, 1957, pp. 253–257.

Borka, L., Review on Crystal Polymorphism of Substances in the European Pharmacopoeia. *Pharm. Acta Helv.*, 1 (1991) 1–8.

Borka, L. and Haleblian, J.K., Crystal polymorphism of pharmaceuticals (Review). *Acta Pharm. Jugosl.*, 40 (1990) 71–94.

Haleblian, J.K., Characterization of habits and crystalline modification of solids and their pharmaceutical applications (Review). *J. Pharm.*, 64 (1975) 8,1269–1288.

Kalinkova, G.N. and Dimitrova, L., IR spectroscopic studies of the antibiotic cefamandole nafate. *Vibrat. Spectros.*, 10 (1995) 41–47.

Kalinkova, G. and Ovcharova, G., Changes in crystalline state of Cefazolin Na by lyophilization. *Pharmacia*, 6 (1994) 24–26.

Kalinkova, G., Ovcharova, G. and Gagauzov I., IR-spectroscopic investigations of some β-lactam antibiotics. In Jordanov, B., Kirov, N. and Simova, P. (Eds.), *Recent Developments in Molecular Spectroscopy. Proceedings of the Tenth National Conference on Molecular Spectroscopy with International Participation*. Blagoevgrad, Bulgaria, 29 August to 3 September, 1988. World Scientific, Singapore, 1989, pp. 705–709.

Kalinkova, G.N., Ovcharova, G., Gagauzov I., Krestev, V. and Petrov, L., Comparative IR-spectral studies of different modifications of the antibiotic Cefazolin Na. *J. Mol. Struct.*, 219 (1990) 329–334.

Otsuka, M. and Kaneniwa, N., Effect of grinding on the crystallinity and chemical stability in the solid state of cephalotin sodium. *Int. J. Pharm.*, 62 (1990) 65–73

Pavlova, A.V., Atanasova, T.K., Ivanova, Z.T., Batchvarova, A.S. and Georgiev, M.P. Crystal and noncrystal azlocillin sodium. *Pharmazie*, 43 (1988) 5, 363.

Pikal, M.J., Lukes, A.L., and Lang, J.E., Thermal Decomposition of amorphous β-lactam antibacterials. *J. Pharm. Sci.*, 66, 9 (1977) 1312–1316.

Pikal, M.J., Lukes, A.L., Lang, J.E. and Gaines, K., Quantitative crystallinity determinations for β-lactam antibiotics by solution calorimetry, correlation with stability. *J. Pharm. Sci.*, 67 (6) (1978) 767–773.

Thoma, K. and Serno, R., Physical instability of drugs as a results of polymorphic changes in the crystal structure. *Dtsch. Apoth. Ztg.*, 124 (1984) 253–259.