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COMMUNICATIONS

An observation of polymorphism in pentamidine isethionate

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Abstract—Two forms of pentamidine isethionate have been identified from two commercial samples of the compound. The lower melting form was produced by freeze drying and has a melting point of 133·4°C whilst the higher melting form has a melting point of 192°C. Powder x-ray diffraction studies showed that each modification was crystalline and the infra-red spectra showed differences that could be attributed to polymorphism. It was noted that when the freeze dried material was exposed to the atmosphere it converted to the higher melting form and was hygroscopic. Examination of this compound in a formal polymorphism screen was advocated.

Pentamidine isethionate is an aromatic diamidine that has been found to be useful in the treatment of *Pneumocystis carinii* infections in patients suffering from AIDS (Sands et al 1985; Goa & Campoli-Richard 1987). Although this compound was first synthesized in the late 1930's there have been few reports relating to its physicochemical properties and in particular there have been no reports of the existence of polymorphs for this compound. The following is a report of an observation of polymorphism during the preformulation screening of two commercial sources of pentamidine isethionate.

Materials and methods

Pentamidine isethionate was obtained (a) from the Aldrich Chemical Company Limited, Lot No 052075P and (b) from Lyphomed Inc. as a freeze dried powder, Pentam 300, Lot No 113615. To characterize this material, differential scanning calorimetry (DSC) was performed using a Perkin-Elmer DSC-2C instrument and samples were scanned at 20 K min^{-1} under an atmosphere of nitrogen; thermogravimetric analysis (TGA) was also carried out at 20°C min^{-1} under nitrogen using a Perkin-Elmer TGS 2 instrument. Powder x-ray diffraction studies utilised a Siemens Krystalloflex 4 instrument whose operating conditions were as follows:

Radiation: Cobalt K_α (wavelength 1·78890Å).
Target conditions: 40kV, 20 ma.
Scan speed: 0·5 deg min^{-1}.

Infra-red spectra were recorded with a Perkin-Elmer 1720X infra-red spectrophotometer using diffuse reflectance measurement, on samples dispersed in KBr but not compressed.

Results

The DSC thermal analysis of the two samples showed that the melting point of the freeze dried material was much lower than that of the material obtained from Aldrich. The onset melting temperature of the freeze dried sample was found to be 406·6K (133·4°C) whilst the Aldrich material had an onset temperature of 465·2K (192·04°C). Both melting peaks were sharp (a good indication of purity) and no other thermal events were noted. TGA of these two samples showed that the freeze dried material contained little or no water whilst the pentamidine isethionate obtained from Aldrich showed a weight loss of ≈0·7%. With infra-red spectroscopy, differences were recorded in the 1000–1300 cm^{-1} and 400–800 cm^{-1} regions (Fig. 1). Powder x-ray diffraction analysis of the samples are shown in Fig. 2 and examination of the diffraction patterns shows that although

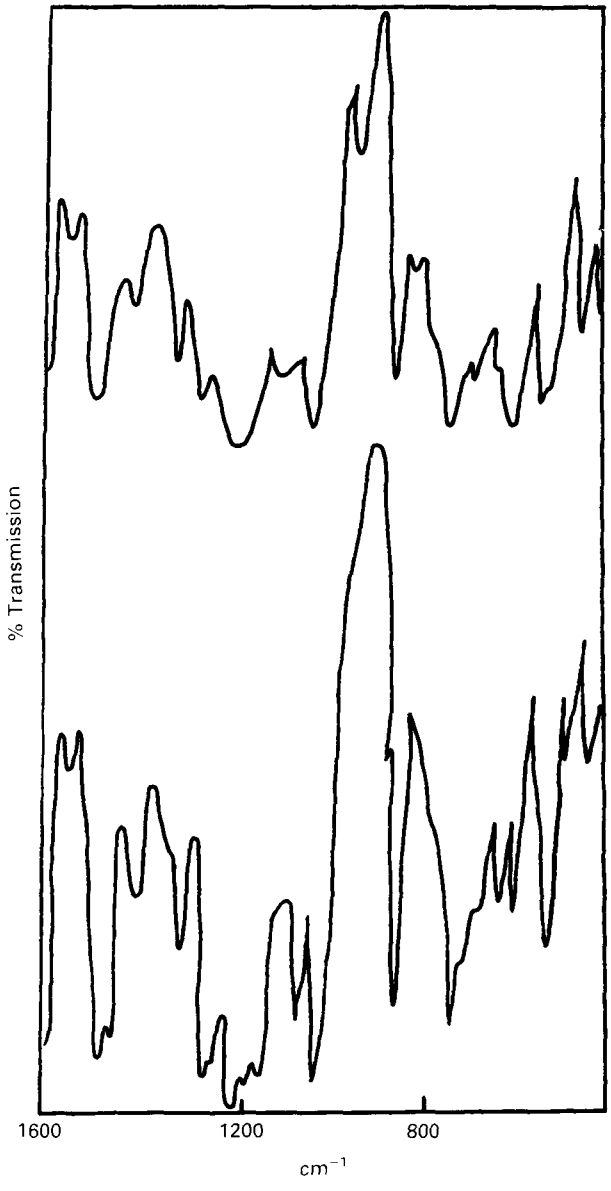

FIG. 1. Infra-red spectra of pentamidine isethionate polymorphs. The top part of the Fig. is the sample obtained from Aldrich and the lower part is the freeze dried sample.

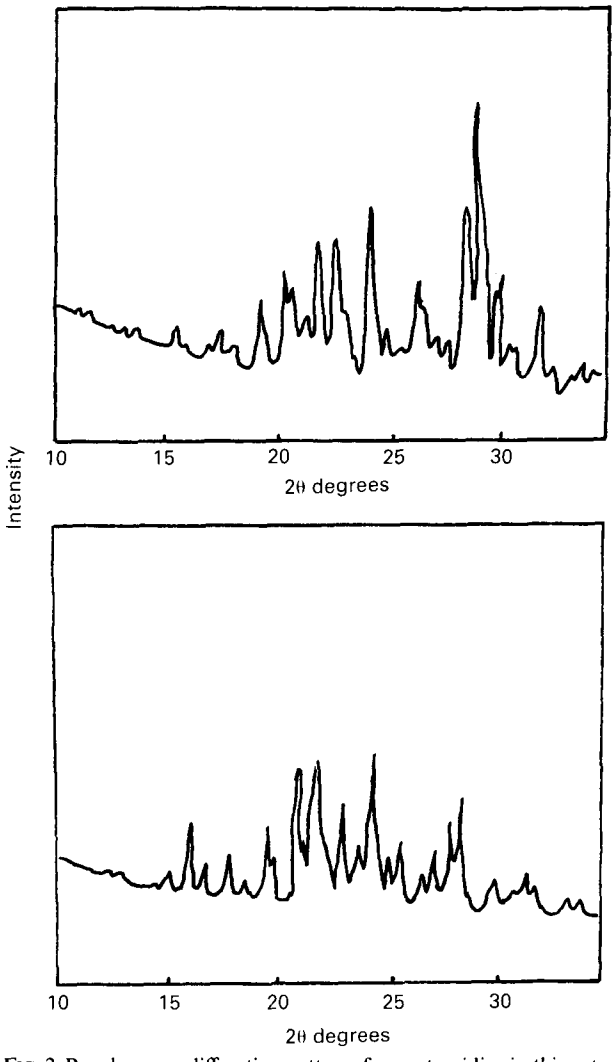

FIG. 2. Powder x-ray diffraction patterns for pentamidine isethionate polymorphs. The top illustration is the sample obtained from Aldrich and the lower illustration is the freeze dried sample.

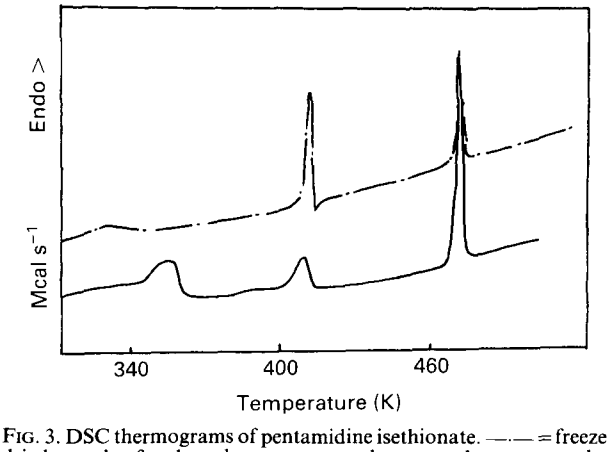

FIG. 3. DSC thermograms of pentamidine isethionate. —·— = freeze dried sample after 1 weeks exposure to the atmosphere. —— = the freeze-dried sample after 3 weeks exposure to the atmosphere.

similarities exist, differences can be found. In combination with the other techniques it can be confirmed that there are two different crystalline modifications of pentamidine isethionate.

Interestingly, DSC performed on the freeze dried sample that had been opened for one week gave a 'mixed' thermogram (Fig. 3) whereby two endotherms were recorded. This is probably due to the higher energy, low melting, polymorph converting to the high melting, more stable, form. After 3 weeks this was more pronounced with the lower melting form being substantially reduced. In addition to this a third endotherm due to the moisture pick up (2·8% by weight using TGA) was observed, although it is thought that this moisture is surface water and not included in the crystal structure, as it is readily dried.

Discussion

It is clear that pentamidine isethionate can exist in at least two polymorphic forms and it may well be possible that other modifications exist. It is well known that lyophilization of compounds results in the formation of different (notably, amorphous) forms (Nakamachi et al 1978; Pikal et al 1978; Saito et al 1982; Pavlova et al 1988). In this case it would appear that freeze drying the compound does not result in the appearance of an amorphous phase. The form produced is, however, unstable and hygroscopic and converts to the higher melting form when exposed to the atmosphere. Although different polymorphic forms of drugs can have different physical properties, such as melting point, solubility, dissolution rate (Haleblian 1975), the fact that the present method of dosage is an intramuscular injection or, more recently, a nebulized solution, makes the biopharmaceutical implications of the occurrence of these forms of slightly less importance. Clearly, other forms of this compound may exist and it would be useful to carry out formal polymorphism screening to try and generate other modifications. This is usually done by recrystallizing, precipitating or concentrating the compound from different solvents at different rates. Alternatively, spray drying or recrystallization from the melt may produce an amorphous form.

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