SOLID FORMS OF HEXAMETHYLMELAMINE (HMM)

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Systemically administered HMM is active against human lung cancer (Hahn, 1983). Reduction of side-effects may be achieved by direct pulmonary delivery of the agent. Our aim was to prepare HMM in forms suitable for administration into airways, particularly to design the aerodynamic properties by modification of the shape of crystals of HMM (Khalik, 1984).

Crystallisation of HMM at low supersaturation from polar solvents (e.g. water, methanol, dichloromethane) yielded predominantly acicular crystals (form I). Under similar conditions, solvents with zero dipole moments (cyclohexane, benzene) produced mainly compact hexagonal crystals (form II). Evaporation of HMM at 182°C followed by rapid condensation at 20°C in a flow system (Khalik, 1984) resulted in fine solid particles (form III) which appeared spherical by electron microscopy.

The purity and identity of all 3 solid forms was confirmed by elemental micro-analysis, UV and ^{1}H NMR spectroscopy. Forms I and II had melting points (m.p.), IR spectra, and single and powder X-ray diffraction patterns identical to the parent material and literature data (Bullen et al., 1972; Van de Vaart-Van Zutphen et al., 1982). Form III was found to have quite different characteristics (see Table 1).

The X-ray powder diffraction and density of form III were compatible with a densely packed structure with cubic symmetry. This was in contrast to the hexagonal crystal lattice of the other forms. None of the above methods indicated the formation of a solvate.

Thus the 'compact' form II is merely a different crystal habit of the previously characterised acicular form I (Bullen et al., 1972) whereas the 'compact' form III is a new 'high energy' polymorph of HMM.

Table 1. Some physical properties of the solid forms of HMM.

Forms	m.p.[a] (C°)	enthalpy of[c] fusion (kJ/mol)	density[e] (kg/dm^3)	aqueous[f] solubility (mg/ml)
I & II	172-174[b]	27.3[d]	1.09-1.12[b]	0.10
III	158	17.9	1.30	0.15

[a]Towson & Mercer, Electrothermal m.p. apparatus; [b]range of [d]values for solids crystallised from 22 solvents; [c]Perkin-Elmer DSC2 apparatus; [d]value for the parent material; [e]floatation for forms I & II, air comparison pycnometry (Beckman Model 930) for form III and two samples of forms I & II; [f]0.1M phosphate buffer, pH=7, 25°C, with no significant differences between agitation for 4 and 48 hours.

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