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# Does aspirin exist in polymorphic states?

Whether various polymorphic states of aspirin actually exist has been commented upon recently by Mitchell, Milare & others (1971) and by Pfeiffer (1971).

Mitchell & others (1971), using X-ray diffraction procedures and infrared spectra techniques (Nujol and attenuated total reflectance), were unable to demonstrate polymorphic differences in aspirin crystals as reported by Tawashi (1968). Based on Tawashi's evidence (1968 & 1969), Pfeiffer (1971) doubted whether true aspirin polymorphs had been prepared. He suggested the need for more explicit directions for preparation of aspirin polymorphs and additional evidence for identification of their presence.

Using the many analytical techniques available, confirmation of the formation of the polymorphs described by Tawashi (1968) was attempted. Samples of aspirin were recrystallized from 95% ethanol and n-hexane, following his procedure.

Aspirin (Merck U.S.P.) was saturated in hot 95% ethanol; upon cooling, large crystals were formed with a melting range of 139–142°. When dried *in vacuo* at room temperature and powdered, these crystals gave a broad melting point range of 126–137°. Following the same procedure, aspirin was likewise crystallized from n-hexane. Small needle-shaped crystals were obtained which gave a melting point of 127–133°. The melting points were determined by a hot stage microscope. Differential thermal absorption curves of these compounds showed melting points of 139° and 142°, respectively.

The crystals from ethanol were thick prisms tending to occur in clusters. Those from n-hexane were very thin blades, rods and needles. The original Merck aspirin material consisted of crystal fragments apparently produced by powdering longer crystals. They resembled the crystals from ethanol more than those from hexane and melted over the range 125–135°.

In spite of these differences in external habits and melting points, these samples of aspirin exhibited identical optical and spectral properties. The principal refractive indices were found to be $\alpha$-1·505, $\beta$-1·645, and $\gamma$-1·655 for the original sample and for the crystals obtained from both solvents. The infrared spectra of both mulls and KBr discs were indistinguishable, in agreement with the findings of Mitchell &

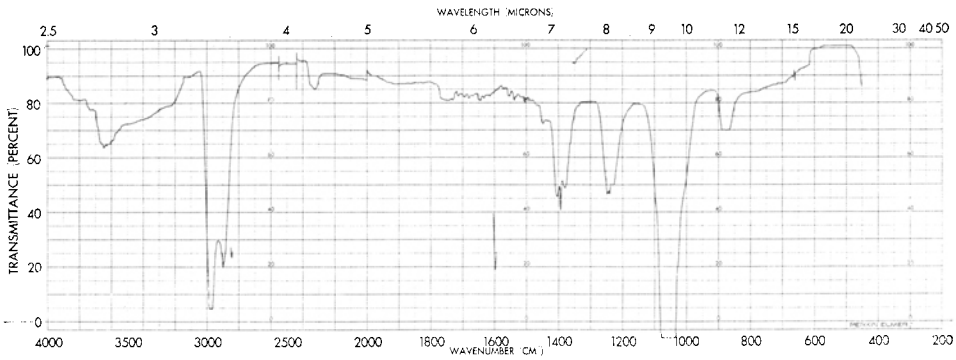


FIG. 1. Ethanol vapour curve obtained by heating aspirin crystals formed in 95% ethanol.

others (1971). Similarly, the X-ray diffraction patterns showed no differences between crystals obtained from 95% ethanol or n-hexane.

Samples of the crystals prepared from each of the solvents were placed in 10 ml glass-stoppered flasks and were heated on a steam bath for approximately 20 min. The glass stoppers were then removed and the air space above the crystals was immediately sampled with a hypodermic syringe, injected into 10 cm evacuated gas cells, and the infrared spectra obtained, as in the method of Schwartzman, Sullivan & Sarnoff (1967). Fig. 1 shows the characteristic spectrum of ethanol vapour obtained when aspirin recrystallized from this solvent was treated as described. It has not yet been established whether the ethanol is present on the surface of the recrystallized aspirin, is trapped interstitially, or is due to hydrogen bonding. No hexane was detected from crystals formed in this solvent.

It is generally accepted that true polymorphism results in distinct optical and spectral properties (see the review by Habelian & McCrone, 1969). The data presented here are entirely negative in these respects.

The evidence accumulated agrees with the findings of Pfeiffer (1971) and questions the formation of aspirin polymorphs. We believe that the different crystal habits were caused by the two solvents used for crystallization. The dissimilar melting points are probably due to the poor transfer of heat caused by the larger crystal size or to possible crystal defects.

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