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LETTERS TO THE EDITOR

The polymorphism of aspirin

Mitchell & Saville (1967) demonstrated that various samples of commercial aspirin have different rates of dissolution. Subsequently, Tawashi (1968, 1969) has reported the existence of aspirin in two polymorphic forms (designated Forms I and II). During the course of present work concerned with the tabletting characteristics of various polymorphic forms of drugs, we have been able to identify several aspirin polymorphs in addition to those already reported. Table 1 shows the conditions under which the polymorphs were obtained.

Confirmatory evidence that all the samples examined were aspirin and differed only in crystalline form is afforded by the fact that no differences could be detected in their ultraviolet spectra when dissolved in ethanol (determined using a Unicam SP800 recording spectrophotometer).

A Perkin-Elmer Differential Scanning Calorimeter DSC-1 equipped with an effluent analyser was used for the thermal analysis of the polymorphs. Samples weighing between 2 and 10 mg were analysed using a scanning rate of 8° min^{-1}. No traces of solvent of crystallization were detected by the effluent analyser when any of the aspirin samples were fused. This therefore excludes the possibility that the samples were solvated forms of aspirin. The DSC traces for the six polymorphs are shown in Fig. 1.

A Kofler hot stage microscope was used to confirm the melting points of the polymorphs. The results are shown in Table 1. The instrument was also used to observe solution phase transformations of pairs of polymorphs. The solvent for this work was n-pentanol saturated with one component of the particular polymorph pair under study. Some of the phase transformations are summarized in Table 2.

Since different polymorphs have different crystal packing conditions, it is to be expected that they will have different true densities. Density determinations were made at 20° using a specific gravity bottle with a displacement medium of light liquid paraffin. Table 1 contains the results of this work.

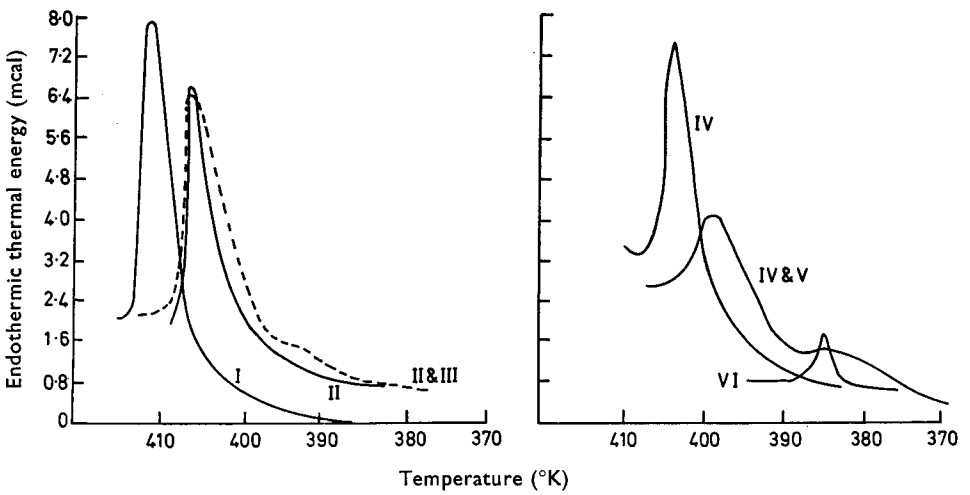

FIG. 1. DSC traces of the six polymorphs of aspirin.

Table 1. *Methods of preparation and physical characteristics of aspirin polymorphs*

Method of preparation	Form nomenclature	Melting point (°C) DSC	Melting point (°C) Hot stage microscope	Density at 20° C (g ml^{-1})
Slow recrystallization from 96% ethanol at 20°	Form I	135	133	1·40
Slow recrystallization from n-hexane at 0°	Form II	129	128	1·50
Slow recrystallization from n-hexane at 20°	Form II & Form III	123 & 114	124 & 115	*
Slow recrystallization from n-octane at 20°	Form IV	123	121	1·36
Slow recrystallization from n-octane at 0°	Form IV & Form V	119 & 100	118 & 100	*
Sublimation of aspirin vapour under vacuum	Form VI	108	110	1·29

* Not possible to isolate polymorphs and make density determinations.
The melting points of polymorphs prepared by Tawashi (1968) were Form I 143° and Form II 125°.

Table 2. *Solution phase transformations of polymorph pairs at 20° C in n-pentanol*

Pair of polymorphs examined	Transformation observed
Form I + Form II	Form II ⟶ Form I
Form II + Form III	No transformation
Form I + Form IV	Form IV ⟶ Form I
Form II + Form IV	Form II ⟶ Form IV

X-ray powder diffraction (Phillips PW 1009/30) using nickel-filtered copper radiation was also performed on the polymorphs. However, only minor differences in the number and intensity of the lines in the diffraction patterns were observed.

The aspirin polymorphs were stable in the presence of moisture and upon storage. Grinding of the polymorphs in a Glen Creston micro-ball mill had no effect with the exception of Form III that was transformed to Form II.

Further work is continuing on the characterization of the polymorphs using dissolution techniques.

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