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REFERENCES

ATTWOOD, D., ELWORTHY, P. H. & KAYNE, S. B. (1969). *J. Pharm. Pharmac.*, **21**, 619–620.
ATTWOOD, D., ELWORTHY, P. H. & KAYNE, S. B. (1970). *J. phys. Chem. Ithaca*, **74**, 3529–3534.
BECHER, P. (1962). *Ibid.*, **66**, 374–375.
CERDAS, J., CARLIER, A., PUISIEUX, F. & LE HIR, A. (1968). *Annls pharm. fr.*, **26**, 239–244.
COLL, H. (1969). *J. am. Oil Chem. Soc.*, **46**, 593–596.
COLL, H. (1970). *J. phys. Chem. Ithaca*, **74**, 520–528.
THAKKAR, A. L., KUHN, P. B. & HALL, N. A. (1967). *Am. J. Pharm.*, **139**, 122–125.
WEIBULL, B. (1960). *Proc. 3rd Int. Congr. Surf. Activ., Cologne*, **3**, 121–125.

Further evidence on the question of polymorphism in aspirin

Several reports have recently appeared describing the preparation and properties of polymorphic forms of aspirin (Tawashi, 1968; Summers, Carless & Enever, 1970). Other reports have however suggested that the evidence for polymorphism so far presented is inconclusive and that the differences which exist between the various forms could be due to differences in crystal size and habit (Pfeiffer, 1971) or to crystal defects (Mitchell, Milaire & others, 1971). We wish to report some observations we have made during an investigation into the biopharmacy of salicylates which may help in resolving the conflict between these various viewpoints.

Preliminary studies using the procedures of Tawashi (1968) and Summers & others (1970) suggested that some salicylic acid was formed on dissolving aspirin in non-aqueous solvents. These observations were further investigated by equilibrating excess dry aspirin at 20° in sodium dried n-hexane and n-octane. Samples of solution were removed at various times and their absorbance measured over the range 270–320 nm using an SP 500 spectrophotometer. After 400 h 40 μg/ml of aspirin and 20 μg/ml of salicylic acid were found in the n-hexane solution and 30 μg/ml of aspirin and 10·5 μg/ml of salicylic acid in the n-octane using the Extinction Ratio method.

In view of the low solubility of aspirin in n-hexane at 20° it was necessary, in order to obtain an adequate yield, to reflux excess dry aspirin with n-hexane at 68° for 1½–2 h. After filtration, analysis of the hot solution showed the presence of approximately 600 μg/ml of aspirin and 60 μg/ml of salicylic acid. Portions of the hot solutions were allowed to stand at 0° or 20° for 14 h and the resulting crystals collected by filtration. The filtrates were then allowed to evaporate at the same temperatures to approximately a quarter of their original volume. After 200–350 h further samples of crystals were collected by filtration. The properties of the crystals obtained from these experiments are shown in Table 1 together with those of samples prepared by recrystallization from 96% ethanol and by sublimation at 118° onto a cold surface at 17° under various pressures.

The amount of salicylic acid present in the samples was determined both by the Extinction Ratio method in absolute ethanol and by a modification of the B.P.

limit test for salicylic acid in aspirin. The colour produced was measured at 530 nm and the amount of salicylic acid calculated from a calibration curve.

Thermal analyses of the samples were made using a Dupont 900 thermal analyser on 2–3 mg samples heated at 8°/min in air. Differential Thermal Analysis (DTA) peak temperatures are given in Table 1. Infrared spectroscopy showed no differences between the spectra of samples prepared from 96% ethanol and n-hexane.

Mitchell & Saville (1967) showed that samples of commercial aspirin have different intrinsic dissolution rates. The existence of polymorphic forms of aspirin, however, was first reported by Tawashi (1968), the stable form I (m.p. 143°) being obtained by crystallization from 95% ethanol and the less stable form II (m.p. 124°) by slow crystallization from n-hexane at room temperature. Form II dissolved more rapidly than form I and produced higher plasma levels after administration in man (Tawashi, 1969). Differences in the two forms were claimed to persist in dimethylformamide solution (Kildsig, Denbo & Peck, 1971). Summers & others (1970) described six polymorphs of aspirin obtained by sublimation or recrystallization under differing conditions from various organic solvents. These forms had different densities and melting points and underwent phase transformations in solution. Only minor differences were observed in their x-ray diffraction patterns however and Pfeiffer (1971) questioned the conclusion that aspirin polymorphism had been demonstrated. He suggested that the experimental observations could be explained by differences in crystal size and habit or to imperfections and stresses within the crystal. Mitchell & others (1971) agreed that the evidence for polymorphism was inconclusive and repeated their view that the differences could be due to crystal defects.

Table 1 indicates that all samples of aspirin prepared either by recrystallization or by sublimation are likely to contain traces of salicylic acid. The effect of impurities on the physicochemical properties of crystalline materials can vary depending on the

Table 1. *The melting-point and purity of aspirin samples prepared by various methods.*

Method of preparation	Salicylic acid (%) Extinction Ratio method	Salicylic acid (%) Modified B.P. Colour test	Melting point (°C) DTA	Melting point (°C) DSC*
Recrystallization from 96% ethanol at 20°	0·10	0·05	141	135
Recrystallization from a saturated solution at 68° in n-hexane				
After standing for 14 h at 20°†	0·4–1·4	0·4–1·0	135·3–138·6	—
After standing for 14 h at 0°†	0·5–2·4	0·5–2·3	134·0–138·6	—
Slow recrystallization from n-hexane at 20°†	0·6–1·0	0·8–1·0	126–132	123 & 114
Slow recrystallization from n-hexane at 0°†	0·4–2·0	0·4–2·1	128–136	129
Aspirin sublimed at the following pressures (mmHg): 12	60·0	65·0	115	For sublimed aspirin under vacuum mp = 108
1·6	23·9	24·3	115 & 127‡	
0·8	17·7	16·9	114 & 130‡	
0·05	1·3	2·0	136·6	

* The values quoted here were obtained by Summers & others (1970) using a Perkin Elmer Differential Scanning Calorimeter.

† The recrystallization experiments from n-hexane were repeated four times and the ranges quoted are for the two extreme results.

‡ Where two melting points are quoted, two peaks were observed on the DTA analysis.

mechanism of incorporation. An impurity may be captured by the crystal lattice forming solid solutions of various types. In such cases as little as 0·14% may be sufficient to distort the lattice (Khamskii, 1969). Alternatively it may be adsorbed onto internal or external surfaces or be present in the form of separate crystals. Another frequent phenomenon is the modification of crystal habit by impurities (Mullin, 1961). In all these processes the conditions of crystallization play an important role. Varying the conditions in our experiments produced samples with different melting points and different amounts of salicylic acid. Although individual samples were found to melt at a definite temperature, repeating the experiments under the same conditions yielded crystals melting at similar but not identical temperatures. These observations suggest that variations in the amount, location and bonding of the salicylic acid within the crystal can influence the melting point. Furthermore sublimed aspirin containing 16–25% of salicylic acid gave on thermal analysis two distinct peaks suggesting the existence of two or more types of association.

Since all the previously published phenomena attributed to polymorphism could be explained if salicylic acid had been present in the samples, and as significant differences in x-ray diffraction have not been found, it seems more reasonable to interpret the data as being due to the presence of this impurity rather than polymorphism. Further, unless salicylic acid can be excluded from aspirin samples polymorphism will be difficult to prove.

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REFERENCES

KHAMSKII, E. V. (1969). Crystallization from Solutions, New York and London: Consultants Bureau.

KILDSIG, D. O., DENBO, R. & PECK, G. E. (1971). *J. Pharm. Pharmac.*, **23**, 374–376.

MITCHELL, A. G. & SAVILLE, D. J. (1967). *Ibid.*, **19**, 729–734.

MITCHELL, A. G., MILAIRE, B. L., SAVILLE, D. J. & GRIFFITHS, R. V. (1971). *Ibid.*, **23**, 534–535.

MULLIN, J. W. (1961). *Crystallization*, London: Butterworths.

PFEIFFER, R. R. (1971). *J. Pharm. Pharmac.*, **23**, 75–76.

SUMMERS, M. P., CARLESS, J. E. & ENEVER, R. P. (1970). *Ibid.*, **22**, 615–616.

TAWASHI, R. (1968). *Science, N.Y.*, **160**, 76.

TAWASHI, R. (1969). *J. Pharm. Pharmac.*, **21**, 701–702.