Aspirin polymorphism questioned

Aspirin, crystallized under various conditions, has recently been reported to display different melting points (Tawashi, 1968; Summers, Carless & Enever, 1970), heats of fusion (Tawashi, 1969), densities (Summers & others, 1970), and rates of dissolution (Mitchell & Saville, 1967, 1969; Tawashi, 1968). These differences were ascribed in every case to polymorphic behaviour. It seems, however, that this conclusion is not warranted by the submitted evidence, and that other explanations for the observed differences should be considered.

Particularly disturbing is the failure of the supposedly discrete structures, i.e., "polymorphs," to exhibit different x-ray powder diffraction properties. Even the one possible exception—described only as diffraction "differences" by Tawashi (1968)—may well have been due to preferred crystal orientation, inasmuch as two forms of extremely different shape, i.e., prisms and needles, were compared.

Mitchell & Saville (1968) proposed that x-ray diffraction methods failed to distinguish between two forms of aspirin because the forms were mixtures of polymorphs. In view of the fact that the powder diffraction data from commercial aspirin (presumably Form B) is reconcilable with the single crystal data (Smith, 1962), however, their proposal is questionable.

The findings of Summers & others (1970) that there are six polymorphs of aspirin and that these range in density from 1·29 to 1·50 g/ml *but have similar diffraction properties* are not consistent with the usual concepts of crystal structure and polymorphism.

It is unfortunate that the cited authors did not describe their crystals with regard to size and habit; variables that may conceivably have affected the various measurements. For example, differences in size and habit might:

(*a*) Affect the dissolution rate from a pressed disc through differences in capillarity or wetting;

(*b*) affect the determination of melting point and heat of fusion through differences in rates of sublimation and decomposition. Aspirin has a long history of giving trouble in melting point determinations (Hayman, Wagener & Holden, 1925);

(*c*) affect density measurements by variously interfering with the complete filling of cavities by the displacement fluid.

Another proposal consistent with the published observations would be that the crystals somehow differ with regard to imperfections, stresses or finer structural details, but these differences also would not justify the use of polymorphic designations.

Whatever the source of the apparent extra thermodynamic activity exhibited by some of the aspirin crystals, exposure to heat, ultrasound, solvent, etc. could cause them to anneal, grow or ripen; they would thus mimic polymorphic behaviour by reverting to a "more stable" form but would not undergo changes in their routinely determined x-ray diffraction properties.

In the interest of preserving the meaning of the term "polymorphism," it would be helpful if future publications on the subject of aspirin polymorphism were to clarify the questions raised in this letter. Furthermore, all articles claiming the existence of polymorphs should include explicit directions for their preparation and identification.

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REFERENCES

HAYMAN, J. L., WAGENER, L. R., & HOLDEN, E. F. (1925). *J. Am. pharm. Ass. (Sci. Edn)*, **14**, 388–392.

MITCHELL, A. G., & SAVILLE, D. J. (1967). *J. Pharm. Pharmac.*, **19**, 729–734.
MITCHELL, A. G. & SAVILLE, D. J. (1969). *Ibid.*, **21**, 28–34.
SMITH, J. F. (Editor) (1962). *X-ray powder Data File.* Card No. 12–850. Philadelphia: American Society for Testing and Materials.
SUMMERS, M. P., CARLESS J. E. & ENEVER, R. P. (1970). *J. Pharm. Pharmac.*, **22**, 615–616.
TAWASHI, R. (1968). *Science, N.Y.*, **160**, 76.
TAWASHI, R. (1969). *J. Pharm. Pharmac.*, **21**, 701–702.

The aggregation of chlorhexidine digluconate in aqueous solution from optical rotatory dispersion measurements

In our continuing investigations of the optical rotatory dispersion (ORD) and circular dichroism (CD) of optically active surfactants and the possible detection of micelle or aggregate formation by this technique (Bonkoski & Perrin, 1968, 1969; Mukerjee, Perrin & Witzke, 1970), we have for the first time investigated a system in which the optical activity is centred in the counterion rather than the core of the aggregate. The chlorhexidine digluconate solutions chosen for these studies were prepared from the recrystallized base (Ayerst Labs., Inc., Rouses Point, N.Y.) and the theoretical amount of 1,5-gluconolactone in de-ionized water. Heard & Ashworth (1968) have reported a CMC of $6{\cdot}6 \times 10^{-3}$M for chlorhexidine digluconate, but lower values could be extrapolated from their surface tension and conductance data. We have found, using a Beckman Model RC 16B2 conductivity bridge (Beckman Instruments, Cedar Grove, New Jersey), a CMC of approximately $4{\cdot}4 \times 10^{-3}$M at $25{\cdot}0 \pm 0{\cdot}01°$ (Fig. 1A). This value is in good agreement with the value obtained from optical rotatory dispersion measurements (Fig. 1B and 2). In the ORD investigations

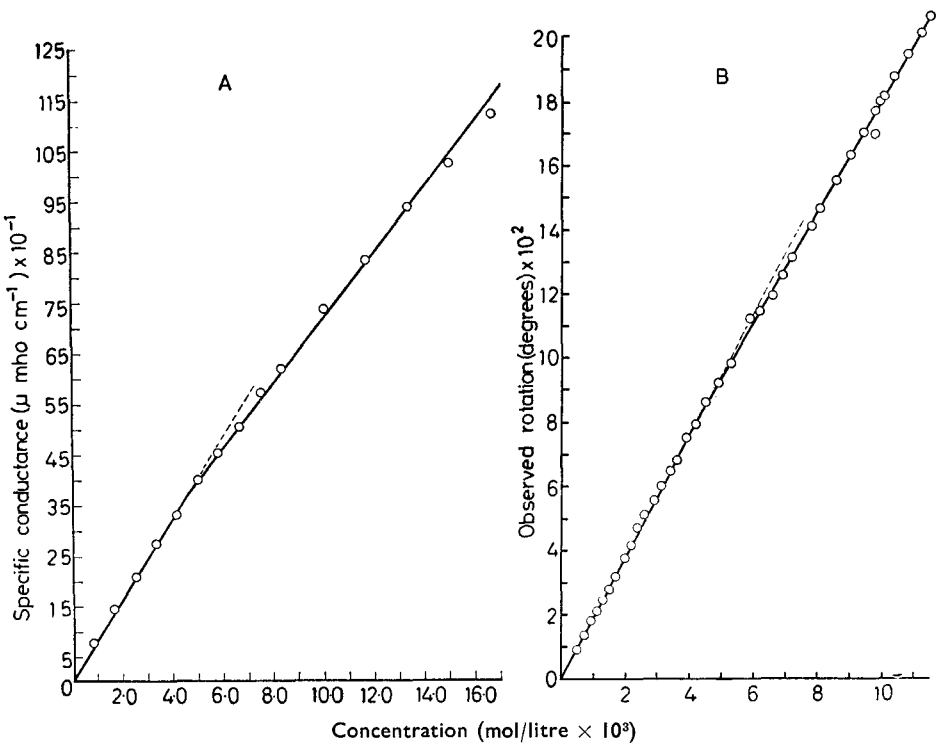

Fig. 1.A. Specific conductances of chlorhexidine digluconate in de-ionized water at 25°. B. Observed rotations at 317·5 nm for chlorhexidine digluconate solutions at 25°.