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LETTERS TO THE EDITOR

Aspirin dissolution: polymorphism, crystal habit or crystal defects

Pfeiffer (1971) has questioned the evidence for the existence of polymorphs of aspirin and has asked that future publications on the subject should clarify a number of questions. We should like to clarify some points in our work.

Mitchell & Saville (1967) demonstrated that various samples of aspirin had different dissolution rates. However the samples examined were obtained from commercial sources and not recrystallized, as stated by Pfeiffer. Moreover since no differences were detected in X-ray diffraction powder patterns, infrared spectra and attenuated total reflectance of infrared we concluded that the variation in dissolution rates was *not* a result of polymorphism. Alternative causes such as differences in size and habit were considered at this time but there was no apparent correlation between these factors and dissolution rate. Hence it was suggested (Saville, 1968) that the variation in dissolution rate may result from differences in the type and number of crystal defects. Subsequently, Tawashi (1968) reported the recrystallization of two polymorphic forms of aspirin. Further studies by Mitchell & Saville (1969), using two samples of commercial aspirin that showed a large difference in dissolution rate, again failed to detect evidence for polymorphism but it seemed possible, assuming the existence of polymorphs, that some commercial samples are likely to be a mixture of polymorphs and hence their X-ray diffraction patterns may be indistinguishable from that of pure polymorphs. The effects of agitation and temperature on dissolution rates showed that the samples had different thermodynamic activities and that the metastable form was capable of rapid reversion to a more stable form. Continued investigation (Griffiths & Mitchell, 1971) has shown that the reversion occurs in the surface layers of the crystal only and that the bulk of the crystal is unchanged. It is not possible to identify the nature of the surface transformation from a kinetic and thermodynamic analysis and X-ray and attenuated total reflection (ATR) measurements failed to reveal any changes after exposure to the dissolution solvent. However, in view of Tawashi's work and the similarity of our results with other studies of transformation accompanying dissolution, it was suggested that the surface-change to a less-soluble form could be due either to the crystallization of a hydrate or a more stable polymorph.

Hydrate formation can now be ruled out since a dissolution pattern indicative of a surface transformation has been demonstrated in a non-aqueous dissolution medium (Mitchell & Milaire, unpublished work). Moreover we have been unable to produce aspirin crystals showing differences in X-ray diffraction powder patterns, infrared spectra (Nujol mull) or ATR using the recrystallization procedures described by Tawashi (1968). The crystals ranged from needles to prisms and it is likely therefore, as suggested by Pfeiffer, that the differences in X-ray diffraction pattern and infrared spectra found by Tawashi are not due to polymorphism but are orientation effects which could result from failure to subdivide the crystals to a sufficiently fine powder.

Summers, Carless & Enever (1970) claim to have found six polymorphs of aspirin, but since these were distinguished only by differences in melting point and density and exhibited only minor differences in X-ray diffraction pattern, we agree with Pfeiffer that this claim is not warranted.

It is well known that crystal faces dissolve at different rates. Hence failure to achieve a requisite degree of size-reduction may be responsible for the variation in dissolution rates of compressed discs prepared from crystals of different habit (Wood; personal communication). It is also conceivable that the phenomenon of reversion can be attributed to dissolution from a rapidly dissolving face and recrystallization onto a more slowly dissolving face. Nevertheless, the single crystal studies of Tawashi show that dissolution from the needle form is much greater than from any face of the prismatic form, and in our work, intrinsic dissolution rates, from a compressed disc of a given aspirin sample, were independent of particle size. Hence differences in crystal habit are unlikely to be the only factor involved in the observed variation in dissolution rates.

Further work to clarify the effect of size and habit is necessary but it is suggested that the effects of crystal defects on dissolution rate should be considered. Line defects, or dislocations, are thermodynamically unstable and Thomas (1970) has emphasized the important, often crucial, role played by dislocations in the reactivity of crystalline solids including such properties as crystal growth and dissolution. Variation in the conditions of crystal growth will affect the type and number of defects in a crystal. It is suggested therefore that the differences in the thermal properties of aspirin recrystallized by Tawashi (1968, 1969) and Summers & others (1970) may also be explained in terms of crystal defects.

This work was supported by a grant from the Medical Research Council of Canada, B.L.M. and R.V.G. gratefully acknowledge the receipt of an M.R.C. summer research scholarship and an M.R.C. postdoctoral fellowship respectively.

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January 18, 1971

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