Microscope Observations of Aspirin Crystallization from Ethanol

R. TAWASHI

Abstract □ Experimental observations of growth steps on aspirin crystals grown from a saturated solution in ethanol are described. The extensive examination of the surface feature of aspirin crystals indicates that the step system is the normal process of growth. From a saturated solution in ethanol, two-dimensional spherulites similar to those in polymers were also obtained; on heating (at 10°/min.), they transformed into aspirin crystals, melting at 125°.

Keyphrases □ Aspirin, crystallization, spherulites—saturated aspirin in ethanol □ Photomicrographs—aspirin spherulites □ Crystallization—saturated aspirin from ethanol

In previous studies, two crystal forms of aspirin were prepared and their dissolution and absorption rates were studied (1, 2). Summers *et al.* (3) recently confirmed these forms, and they characterized four other aspirin polymorphs. Pfeiffer (4) questioned the use of the term polymorphism in aspirin and asked for explicit directions for the preparation and identification of the crystal forms. The purpose of this report is to show that the growth of aspirin form I from saturated solution in ethanol can be understood in terms of Frank's (5) growth mechanism. In addition, it will be shown that two-dimensional spherulites could be prepared from a saturated aspirin solution in ethanol.

EXPERIMENTAL

Materials and Equipment—The materials used in this study were: commercial aspirin USP, ethanol, FD&C Violet No. 1, and 1% gold chloride[1] solution. Photomicrographs were taken with a Polaroid MP-3 Land camera mounted on top of a polarizing microscope. The Mettler FP-2 hot stage was used for determining the melting points.

Observation of Growth Steps—Monoclinic aspirin crystals grow from filtered saturated ethanol solution when left to evaporate slowly (2–3 days) at room temperature (no stirring). These crystals are elongated prismatic tablets, identical to the aspirin form I previously reported (1). Photomicrographs were taken for aspirin crystals still growing in a saturated solution in ethanol (95%) at room temperature. Figure 1 shows a single spiral step originating from the point of emergence of screw dislocation in the aspirin crystal. The step system in the form of a growth hill is seen in Fig. 2. The spiral step system was rendered visible on a number of crystals after etching, for a few seconds, with 1% gold chloride or 5 p.p.m. FD&C Violet No. 1 aqueous solutions. The effect of these etchants on the crystal surface is consistent with findings on crystal poisoning (6, 7) and suggests preferential adsorption of these impurities on the step system of aspirin crystals. The presence of visible growth steps on the surface of aspirin crystals indicates that the step system is the normal process of growth and supports the conclusion made by Glasby and Ridgway (8) that surface reaction could be the rate-controlling step in the crystallization of aspirin from ethanol.

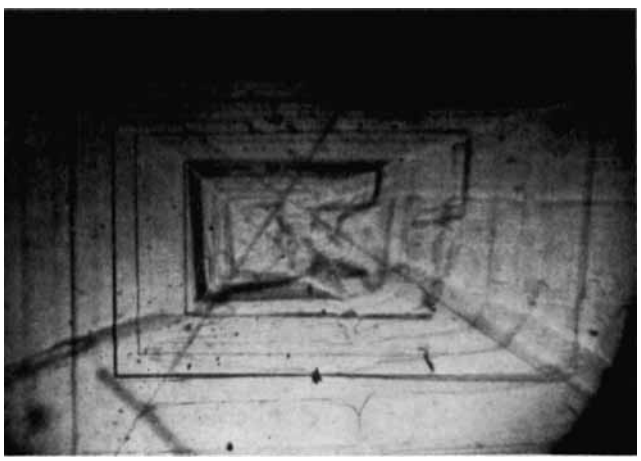

Figure 1—*Growth step system originating from the points of emergence of screw dislocations* (×125).

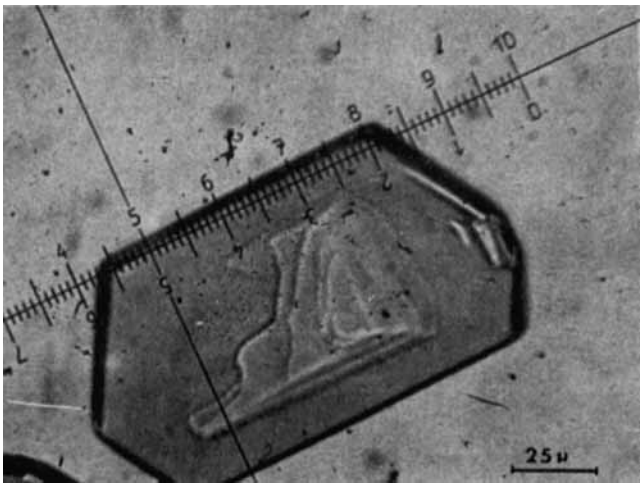

Figure 2—*A growing aspirin crystal showing step system in the form of a growth hill* (×500).

Growth of Aspirin Spherulites (a Mesomorphic Phase)—Spherulites of aspirin were observed under a polarizing microscope when one drop of a fresh, filtered, saturated solution of aspirin USP in ethanol (95%) was spread as a thin film on a clean glass slide, previously washed with ethanol. The spherulites were observed to grow after a few seconds, filling the microscopical field (Fig. 3). The structure was identical in appearance to spherulites obtained from high polymers (9).

Aspirin spherulites exhibited a maltese cross when viewed between crossed polars, where the dark bands were parallel to the polarization directions, indicating that the optical axes were either parallel or perpendicular to the spherulite radii. Larger spherulites (Fig. 4) showed the appearance of fibrillar structures much like those seen for cholesteryl acetate (10) and 2,4,6-trinitrotoluene grown in thin films (11). Qualitative microscopic observation of aspirin spherulites revealed that the spherulites grow radially outward from their center at a rate that increases with decreasing temperature.

Structural changes accompanying the change of temperature were studied, using the Mettler FP-2 hot-stage microscope. On heating at 10°/min., the two-dimensional spherulites were transformed at 124° into needle-like crystals starting from the center of the spherulite. This transformation did not reverse on cooling, and the solid product obtained melted at 125° (10°/min.; Fig. 5).

The growth of aspirin into two-dimensional spherulites is an interesting phenomenon, because substances of low molecular

[1] British Drug House Pharmaceuticals, Dorval, Quebec, Canada.

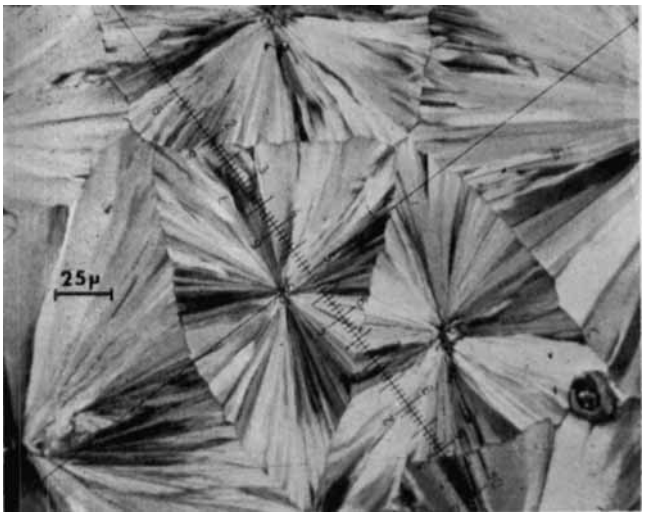

Figure 3—*Photomicrograph between crossed polars for spherulites of aspirin at room temperature (×500).*

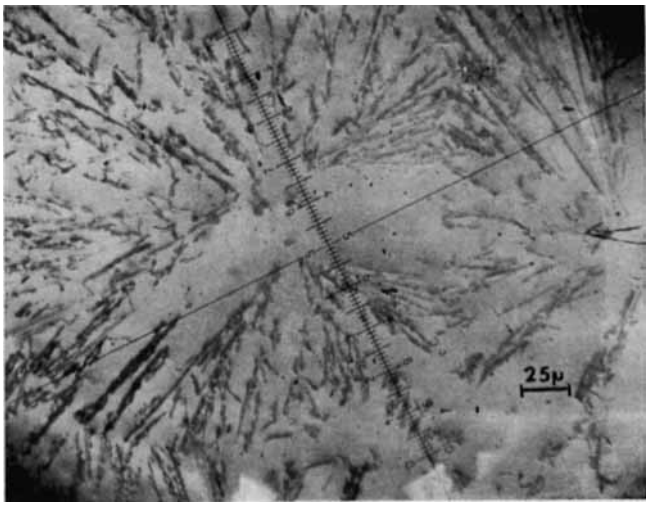

Figure 5—*Photomicrograph from the same field (Fig. 4) after heating to 124° (at 10°/min.), showing the transformation to solid crystalline needles of aspirin.*

weight like aspirin do not normally crystallize in this way. However, there are special circumstances when high supersaturation and a high viscosity of the crystallization medium can favor the formation of spherulites (12). These conditions are likely to be met when the aspirin solution is spread as a thin film on the glass slide, where the available surface for evaporation increases, and the solvent mass transfer rate becomes an important factor in crystallization.

On the basis of this observation, one might be tempted to conclude that variation in thermal and dissolution characteristics of commercial aspirin could be attributed to the presence of aspirin spherulites on the surface of commercial aspirin crystals. The formation of these spherulites on the surface of aspirin crystals takes place immediately after separation of the crystals from the crystallizing solvent and/or during the drying period. The entirely different grain structure on the surface of aspirin crystals can lead to an appreciable change in the response of commercial aspirin to thermal stress and to mass transfer in dissolution. This view is supported by the following:

1. Commercial aspirin USP has a long history of giving trouble in melting-point determination. Freshly crystallized aspirin from ethanol is a monoclinic prismatic crystal, which melts at 143–144° (2°/min.) if the crystal is washed with hexane before the melting point is determined. This value agrees with the work of Wheatley (13) and with the previously reported value (1).

2. There is a depression in the melting point of at least 4° if the same crystals are left for 48 hr. in the solution or if the crystals are not washed from the adhering mother liquor before determination of the melting point. The formation of aspirin spherulites on the crystal surface and the appearance of a new type of grain structure could explain the wide variation in melting point.

3. A recent study on the dissolution behavior of commercial aspirin USP by Griffiths and Mitchell (14) demonstrated that bulk concentration increased rapidly and showed an initial peak before the equilibrium solubility was reached. The authors suggested that phase change in the surface layers of aspirin crystals is responsible for the unusual dissolution patterns obtained and indicated that the nature of surface transformation cannot be established from the kinetic and thermodynamic data.

Experimental study on spherulite growth in aspirin and a complete understanding of spherulite formation will be helpful in interpreting the dissolution characteristics and thermal properties of commercial aspirin crystals.

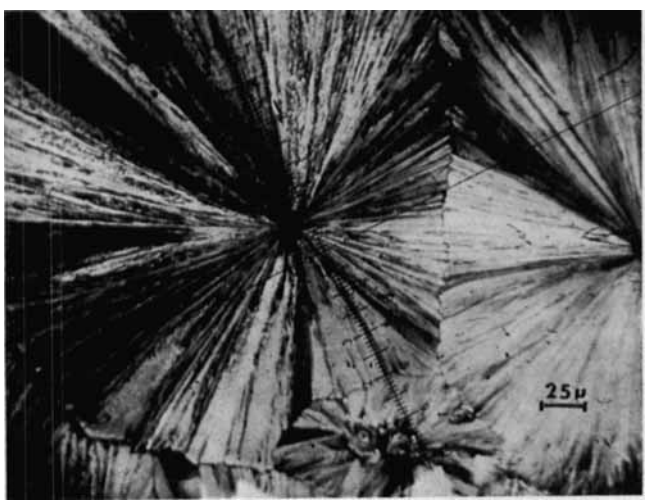

Figure 4—*Center of aspirin spherulites with a higher growth rate obtained by cooling.*

REFERENCES

(1) R. Tawashi, *Science*, **160,** 76(1968).
(2) R. Tawashi, *J. Pharm. Pharmacol.*, **21,** 701(1969).
(3) M. P. Summers, J. E. Carless, and R. P. Enever, *ibid.*, **22,** 615(1970).
(4) R. R. Pfeiffer, *ibid.*, **23,** 75(1971).
(5) F. C. Frank, *Discuss. Faraday Soc.*, **5,** 48, 67(1949).
(6) J. Piccolo and R. Tawashi, *J. Pharm. Sci.*, **59,** 56(1970).
(7) *Ibid.*, **60,** 59(1971).
(8) J. Glasby and K. Ridgway, *J. Pharm. Pharmacol.*, **20,** 94S(1968).
(9) P. Geil, "Polymer Single Crystals," Interscience, New York, N. Y., 1963.
(10) M. B. Rhodes, R. S. Rorter, W. Chu, and R. S. Stein, *Mol. Cryst. Liquid Cryst.*, **10,** 295(1970).
(11) M. C. Chick, W. Connick, and B. W. Thorpe, *J. Cryst. Growth*, **7,** 317(1970).
(12) F. P. Price, *Polym. Sci.*, **37,** 71(1959).
(13) P. J. Wheatley, *J. Chem. Soc.*, **1964,** 6036.
(14) R. V. Griffiths and A. G. Mitchell, *J. Pharm. Sci.*, **60,** 267 (1971).

ACKNOWLEDGMENTS AND ADDRESSES

Received February 8, 1971, from the *Faculty of Pharmacy, University of Montreal, Montreal 101, Canada.*

Accepted for publication May 21, 1971.

The author thanks Mr. J. Pauwels for his technical assistance and the Medical Research Council of Canada for supporting this investigation.