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Aspirin: Dissolution Rates of Two Polymorphic Forms

Abstract. *Two polymorphic forms of aspirin were characterized; the rates of dissolution of single crystals and of tablets were studied. One form dissolves 50 percent faster than the other.*

In evaluating the drug action (*1*) of different formulations of aspirin, crystal modification and the possible effect of polymorphism on drug availability (*2*) have frequently been disregarded. I now report that the rates of dissolution of two polymorphic forms of aspirin were different, regardless of whether the measurement was made from a single crystal or from a tablet.

Polymorph I was prepared by slow crystallization at room temperature from a saturated solution of commercial aspirin (U.S.P.) in 95 percent ethanol. The melting point (determined with a Kofler hot-stage microscope) was 143° to 144°C, a value which is in agreement with the monoclinic crystal structure determined by Wheately (*3*). Polymorph II was prepared by slow crystallization from a saturated solution of commercial aspirin (U.S.P.) in *n*-hexane at room temperature and melted at 123° to 125°C. Both forms meet the U.S.P. specifications.

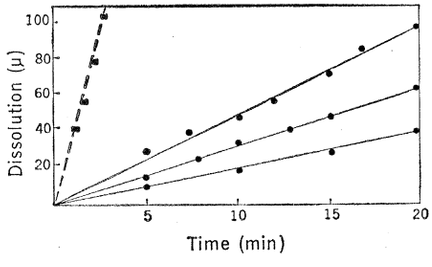

Fig. 1. Single-crystal dissolution as a function of time. Circles, form I; rectangles, form II.

X-ray diffraction (powder method) with nickel-filtered copper radiation and infrared spectra (Nujol mull) were used to characterize the two crystalline forms. Differences in x-ray diffraction patterns and in absorption spectra (not shown here) indicated different arrangements of aspirin molecules in the crystal lattice of each form.

The linear rate of dissolution was measured by a direct optical method (*4*). A single crystal of aspirin 400 to 600 μ was fixed into a rubber slit and placed in a jacketed dissolution cell. The cell was filled with 400 ml of distilled water and kept at a constant temperature of 30°C. Stirring was maintained at 150 rev/min by a synchronized motor. The distance between the two parallel faces of the mounted crystal and the boundary movement across each face were measured as a function of time. Measurements were done by means of a microscope fitted with a filar micrometer. The optical system could differentiate boundary movement in the order of 2 μ, and dissolution data were reproducible within $\pm$ 5 percent for ten determinations. Figure 1 demonstrates the degree of dissolution in microns as a function of time for the two crystal forms. The other two axes in form II could not be measured owing to limitation of the optical system to measure with accuracy the boundary movement in a thin needle-like crystal.

With slight modifications, the dissolution rate of aspirin tablets were studied with the same apparatus. Aspirin tablets from each polymorphic form were prepared under the same pressure and having the same diameter, 1.88 cm; no fillers, lubricants, or antiadhesives were used. The tablet was then placed at one end of a short glass tube having the same inside diameter as the diameter of the tablet, the other end of the tube was filled with molten, white beeswax and left to set; wax was used to hold the tablet.

At zero time, the tube was introduced into the dissolution cell containing 400 ml of distilled water at 30°C. Samples of the water were then pipetted out at specified time intervals and assayed spectrophotometrically at 282 nm. The assay was reproducible within $\pm$ 2 percent for six determinations. Figure 2 shows the amount (μg/ml) dissolved as a function of time for forms I and II. Their initial slopes are 0.862 and 1.350, respectively.

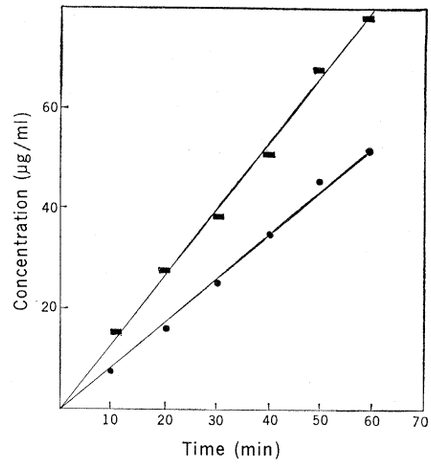

Fig. 2. Dissolution rates of aspirin from tablet. Circles, form I; rectangles, form II.

In the single-crystal comparison, dissolution occurred with different velocities along the different axes (anisotropic). The average rate for form II was evidently greater than that for form I, in spite of the unknown contribution of the other two axes in the dissolution process. Tablets prepared from form II dissolved about 50 percent faster than those of form I, and the results obtained are in agreement with studies on single crystals. From this limited study, it appears that polymorph II has a greater thermodynamic activity and exhibits a higher dissolution rate than polymorph I. Polymorph I was very similar to commercial aspirin (U.S.P.) used in this study, in dissolution rate from tablet and in x-ray diffraction pattern, the only difference being that it was grown from ethanol in nearly perfect crystals, suitable for single-crystal dissolution, while commercial aspirin U.S.P. consisted of crushed, irregularly shaped crystals.

R. TAWASHI

Faculty of Pharmacy,
University of Montreal,
Montreal, Quebec

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