USP Dissolution Test I: Adequacy of Mixing

Keyphrases □ Dissolution apparatus—effect of sampling depth, temperature, and time on results □ Apparatus, dissolution—effect of sampling depth, temperature, and time on results

To the Editor:

This laboratory is presently engaged in a study aimed at characterizing the hydrodynamics (1, 2) of the USP dissolution apparatus. Phenomena have been observed akin to those reported by Withey (3) and Withey and Bowker (4), who found that "spurious results could be obtained if its sampling depth is varied." This communication assesses the seriousness of this problem and suggests a means of minimizing it.

Three pellets of pure oxalic acid dihydrate, 1.113 cm in diameter and 0.38 cm in thickness, were subjected to dissolution in a USP dissolution apparatus operated at 50 rpm in 900 ml of 0.1 *N* HCl at 25°. It was visually apparent that there was a schlieren effect; one can actually observe the discrete schlierens of oxalic acid solution move out into the liquid, sink somewhat, and then disperse. The results are shown in the lower curve in Fig. 1.

Four experiments were run in which the dissolution was carried out for 150 sec, the basket was removed, and the entire 900 ml of liquid in the dissolution vessel was assayed. This procedure was repeated at other time points, and the results are shown in the top curve in Fig. 1. Point-to-point *t*-comparisons and rank tests showed that the two sets of data differed significantly at the 99.9% confidence level.

The described tests were performed at 25°, and the sampling was carried out close to (1 cm below) the surface. The problems encountered at 25° probably would occur at 37° as well and be even more pronounced. The chosen point of sampling, of course, emphasized differences due to improper mixing. To establish the effect of temperature and sampling points, the experiments were repeated at 37° at various sampling points (Table I).

The USP description (5) states that "one of the outer ports *may* be used for insertion of a thermometer. Samples *may* be removed . . . through the other two ports." No actual dimensions or positioning details are given other than the drawing in the cited reference. Therefore, experiments were carried out (at 37°) with a setup that dimensionally matched the drawing in the USP.

Two experiments were performed (Table I). In one, a syringe was attached to the sampling tube and the dissolution was carried out with air in the dip tube (the air was there because the syringe was attached prior to the addition of liquid). This method is denoted USP-2 in Table I. In the other experiment (USP-1 in Table I), the syringe was added after the liquid was added to the vessel, so the liquid level in the dip tube matched that of the liquid in the vessel during dissolution. In this latter setup, a stagnant column of liquid will be sampled. In most sampling situations, the concentration at the sampling point will not equal the average concentration of the liquid in the vessel. If the volume of liquid is multiplied by the concentration, the amount obtained from the sampling will differ from the amount actually dissolved.

Table I—Concentrations Multiplied by Volume for Sampling at Various Points at 37° Compared with Amounts Actually Dissolved

Seconds	Position	Volume × Concentration, mg: At Sampling Point[a]	Volume × Concentration, mg: Entire Content Assayed[a]
120	0.5 cm below surface	57[a]	455
120	1 cm below surface	284[a]	455
120	2 cm above bottom	611[a]	455
120	At bottom	597	455
120	USP-1	270[a]	470
120	USP-2	398[a]	470
240	0.5 cm below surface	583[a]	796
240	1 cm below surface	753	796
240	2 cm above bottom	867[a]	796
240	At bottom	870[a]	796
240	USP-1	754[a]	839
240	USP-2	810	839

[a] Assays shown are averages of duplicate experiments. The sample standard deviation is 20 mg; on a two-way comparison, differences over 63 are significant on the 95% level.

This fact does not *per se* invalidate the test, although it places several restrictions on it, some rather severe. If the position and dimensions of the thermometer and sampling tube are defined carefully, curves can be obtained that will be reproducible. If such curves can be shown to correlate with *in vivo* data, then the test conceivably may be used as a control tool (6). However, dimensional specificity would be a necessity in such a case, as would duplication validation between apparatuses to be used.

The method denoted USP-2 in Table I gives the results closest to the actual content. It is felt that continuous monitoring by pumping liquid continuously through a flowcell comes close to this condition, since it eliminates the stagnant column of liquid in the sampling tube.

The use of a highly soluble substance (oxalic acid dihy-

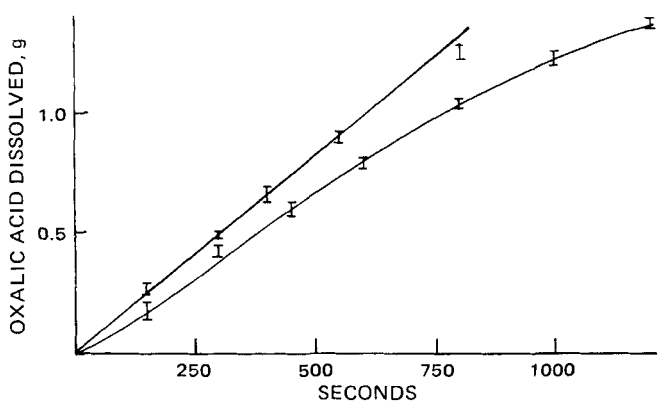

Figure 1—*Results from dissolution of oxalic acid dihydrate pellets in USP dissolution apparatus operated at 25° and 50 rpm. Key: upper curve, entire liquid mass assayed at each time point; and lower curve, samples taken 1 cm below surface.*

drate) accentuates the positional difference in concentration. The differences, furthermore, will be most pronounced in the beginning of the curve. Eventually, of course, all material will dissolve (provided the amount of liquid suffices) and molecular diffusion will provide a state of complete mixedness at very high time values.

The described phenomena were found with dissolution at higher revolutions per minute as well, although not to the same extent. They offer an added explanation of why dissolution curves are often sigmoid shaped[1], although a sigmoid shape *per se* should not be taken as a criterion for poor mixing since other factors affect curve shape.

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(5) "The United States Pharmacopeia," 19th ed., Mack Publishing Co., Easton, Pa., 1975, p. 651.
(6) L. J. Leeson, *J. Pharm. Sci.*, **62** (4), iv (1973).

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Polymorphic and Dissolution Properties of Mercaptopurine

Keyphrases □ Mercaptopurine—polymorphic form, dissolution rate, differential thermographic and X-ray diffraction analyses □ Polymorphic form—of mercaptopurine, dissolution rate, differential thermographic and X-ray diffraction analyses □ Dissolution rate—polymorphic form of mercaptopurine, differential thermographic and X-ray diffraction analyses □ Antineoplastics—mercaptopurine, polymorphic form, dissolution rate, differential thermographic and X-ray diffraction analyses

To the Editor:

Mercaptopurine is an effective purine antagonist (1) that has significant activity against human leukemia and other neoplastic disorders. It distributes throughout the body tissues rapidly and is extensively metabolized (2). Upon oral administration, it shows erratic and incomplete absorption (3). Although the structural similarity of mercaptopurine with natural purines makes the mechanism of its absorption complicated, its dissolution rate probably affects its bioavailability in view of its low water solubility.

The purpose of this communication is to report a fast dissolving polymorphic form of mercaptopurine which can be useful in increasing the bioavailability of this compound.

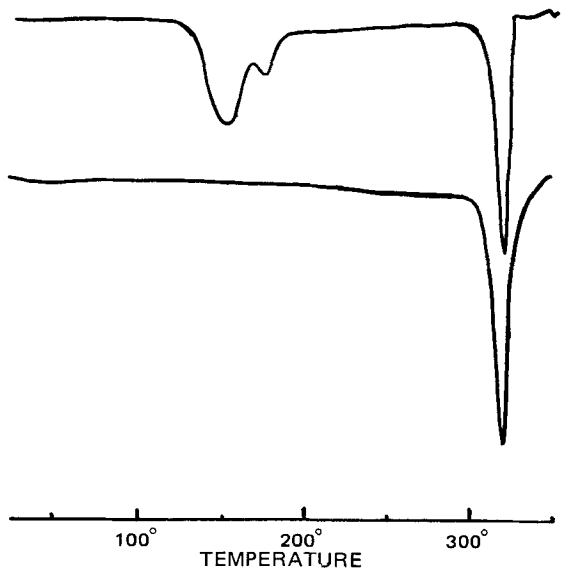

Figure 1—*Differential thermogram of original (top) and heat-treated or rerun (bottom) samples of mercaptopurine.*

The sample of mercaptopurine supplied by the manufacturer[1] yielded a differential thermogram[2] with two endothermic peaks (Fig. 1). The second peak is attributed to the melting of the compound as confirmed by a visual method[3]. The first endothermic peak can be attributed to, among other possibilities, a mercaptopurine polymorph (4). A rerun (Fig. 1) on the same sample showed only one peak corresponding to the final melting point. A similar thermogram with one peak was obtained when the sample was incubated at 225° for 20 min (4), strengthening the possibility of the polymorphic transition observed as the first endothermic peak in the original thermogram.

A sample of the high energy polymorph was prepared by incubating the original drug at 225° for 20 min; then it was subjected to X-ray diffraction analysis[4] (Fig. 2). The

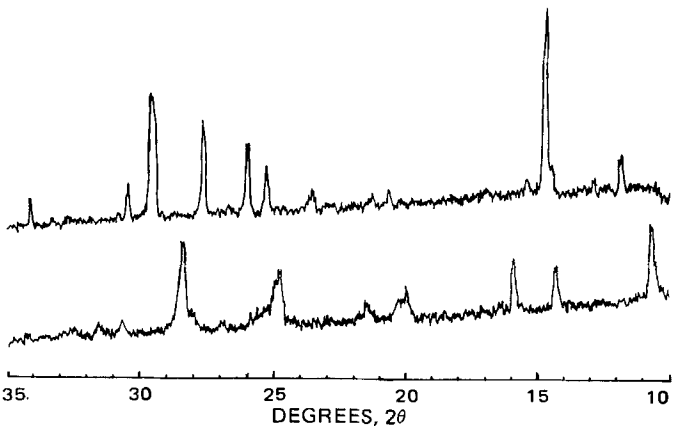

Figure 2—*X-ray diffraction spectra of original (top) and heat-treated (bottom) samples of mercaptopurine.*

[1] Supplied by Burroughs Wellcome Co., Research Triangle Park, N.C.
[2] DuPont 990 thermal analyzer, E. I. du Pont de Nemours & Co., Wilmington, Del.
[3] Arthur H. Thomas Co., Philadelphia, Pa.
[4] Picker X-ray diffractometer.