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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Received October 28, 1976.
Accepted for publication January 1, 1977.
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[1] Unpublished results.

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.

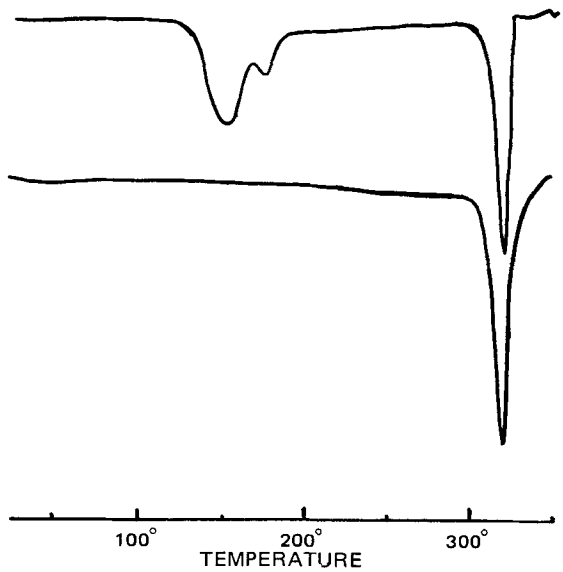

Figure 1—*Differential thermogram of original (top) and heat-treated or rerun (bottom) samples of mercaptopurine.*

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

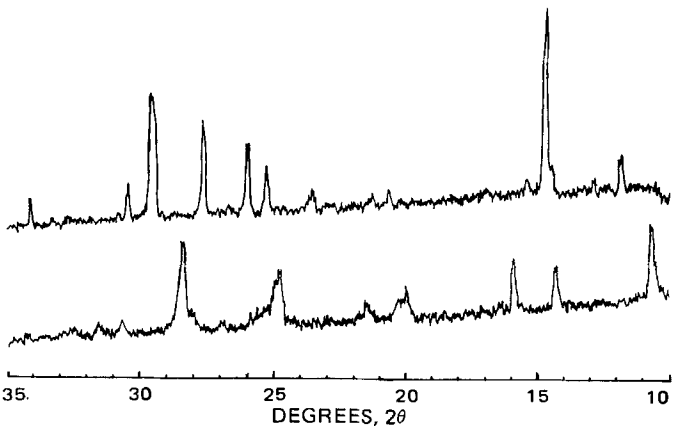

Figure 2—*X-ray diffraction spectra of original (top) and heat-treated (bottom) samples of mercaptopurine.*

[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.

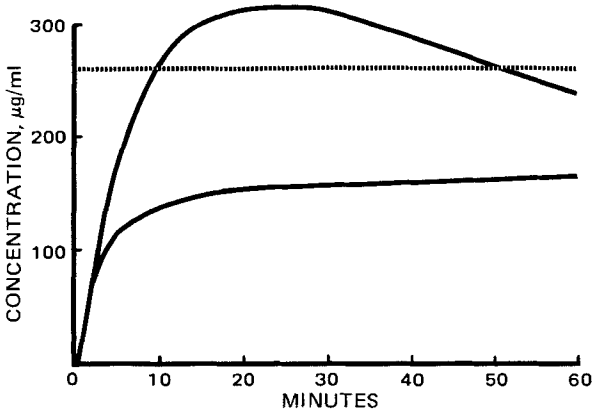

Figure 3—*Dissolution of high energy (top) and low energy (bottom) polymorphs of mercaptopurine. Broken line indicates equilibrium solubility at 37° in water.*

powder X-ray diffraction spectrum of the heat-treated sample was entirely different from that of the original compound, confirming the existence of at least two polymorphic forms. The IR spectra[5] were also different, with increased CH stretching and bending and additional CN and CC stretching and CH rocking in the heat-treated, high energy polymorphic form.

The purpose of this study was to show that a higher energy, relatively stable form of mercaptopurine can exist compared to the form of the drug used in commercial dosage forms. It is possible that the original compound may itself be composed of several polymorphic forms, especially in view of the peak splitting observed in the thermogram (Fig. 1). This aspect is currently being investigated in our laboratory.

The equilibrium solubilities of the two polymorphic forms were determined by placing excess drug in dialysis tubing[3], which was sealed, placed in an erlenmeyer flask containing 100 ml of distilled water, and equilibrated at 37° for up to 5 days. Prior studies excluded any interactions in the analysis due to leaching from the tubing.

This method allows direct sampling of the solution without filtration, which can result in significant loss due to adsorption. The solutions were analyzed spectrophotometrically[6] and gave the identical solubility value of 259.2 ± 4.3 μg/ml (mean ± *SEM*) for the two polymorphic forms. This observation, in spite of the differences in energy of the two polymorphic forms, can be attributed to the possible conversion of the high energy form to the low energy form when placed in water, a phenomenon reported for other drugs (5). However, the differences between the dissolution rates can still be observed, depending on dissolution conditions (4).

The dissolution rates of the two polymorphic forms were determined in water at 37° using a membrane filtration[7] method, which has often been shown to correlate better with *in vivo* dissolution rates and absorption (6, 7). Initial dissolution rate studies showed (Fig. 3) that the release from the high energy polymorph was twice that obtained from the low energy polymorph, resulting in supersaturation of the solution. These initial dissolution rate data (up to 20 min) showed an excellent log-linear relationship ($r > 0.98$) with corresponding rate constants of 0.25 and 0.16 min^{-1} for the high and low energy polymorphs, respectively. However, if the dissolution was continued for up to 1 hr, the high energy polymorphic form decreased in concentration, indicating precipitation and conversion to the low energy polymorph.

The effect of the nature of the medium on the dissolution rate and *in vivo* bioavailability aspects are currently being investigated in our laboratories.

[5] Perkin-Elmer IR spectrophotometer.

[6] Beckman DBGT spectrophotometer, Beckman Instrument Co., Fullerton, Calif.

[7] Sartorius membrane filter solubility simulator, Sartorius Filters, Inc., San Francisco, Calif.

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Received November 8, 1976.
Accepted for publication January 18, 1977.
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Absolute Availability of Lithium

Keyphrases □ Lithium carbonate—bioavailability, calculations based on perturbation of renal clearance, commercial dosage form □ Bioavailability—lithium carbonate, calculations based on perturbation of renal clearance, commercial dosage form □ Renal clearance perturbation—calculations used to determine bioavailability of lithium carbonate, commercial dosage form □ Antidepressants—lithium carbonate, bioavailability, calculations based on perturbation of renal clearance, commercial dosage form

To the Editor:

It is generally accepted that lithium carbonate is completely absorbed when given orally to humans (1–3). This absorption, however, has not been demonstrated pharmacokinetically by comparison of oral plasma level–time curves with those obtained following intravenous dose administration, due largely to the legal and ethical considerations involved in giving this drug parenterally. It has been shown (4) that the lithium absorption rate can be influenced significantly by formulation differences between different brands. Thus, poorly formulated solid dosage forms may present a potential bioavailability problem for lithium carbonate.

Lalka and Feldman (5) recently reported an indirect method for calculating absolute bioavailability based on perturbation of renal clearance that does not require parenteral data. The purpose of this communication is to report the absolute bioavailability of one commercially