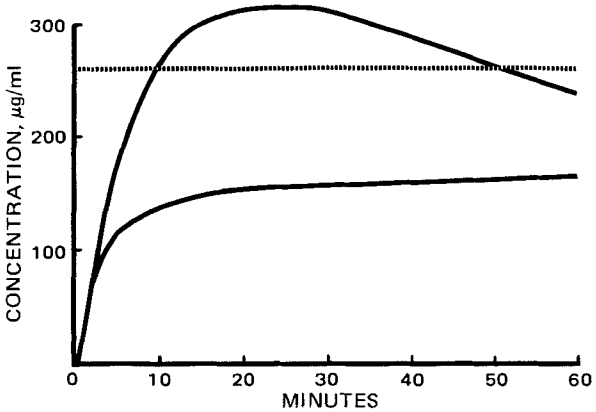


**Figure 3**—*Dissolution of high energy (top) and low energy (bottom) polymorphs of mercaptopurine. Broken line indicates equilibrium solubility at 37° in water.*

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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## 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

Table I—Parameters Used for Calculation of Lithium Availability in Each of Four Subjects

| Subject | $\Delta Cl_R$, liters/hr | $AUC$, mEq/liter × hr | $AUC'$, mEq/liter × hr | $F$ |
|---|---|---|---|---|
| I | 0.644 | 3.337 | 4.448 | 1.043 |
| II | 0.516 | 4.823 | 6.805 | 1.037 |
| III | 0.779 | 3.740 | 5.810 | 0.991 |
| IV | 0.191 | 5.206 | 5.816 | 1.152 |

available dosage form of lithium carbonate using this method.

Four healthy male subjects were given one 300-mg capsule of lithium carbonate[1] under fasting conditions. Plasma concentrations were measured periodically for 30 hr. Three weeks later, the same four subjects ingested 500 mg of chlorothiazide[2] daily for 8 days. On the 8th day, they again were given a single 300-mg dose of lithium carbonate. Details of these experiments were reported elsewhere (6, 7). The coadministration of chlorothiazide and lithium led to an average reduction in renal lithium clearance of 26.5%, thus fulfilling the requirement of renal clearance perturbation (7).

The equation presented by Lalka and Feldman (5) for calculating absolute availability is:

$$F = \frac{\Delta Cl_R}{D}\left[\frac{(AUC)(AUC')}{AUC' - AUC}\right] \qquad \text{(Eq. 1)}$$

where $F$ is the fraction of dose absorbed, $\Delta Cl_R$ is the change in renal clearance that occurs as a result of changes in the experimental conditions, $D$ is the dose administered (8.25 mEq in this case), and $AUC$ and $AUC'$ are the resulting areas under the plasma concentration–time curves for the two experimental conditions.

Values employed in calculating $F$ for each subject are given in Table I along with the calculated $F$ values. As shown, the $F$ value for each subject is very close to unity, indicating that lithium carbonate is completely absorbed under the conditions of these experiments. Thus, we have demonstrated the applicability of this method for determining absolute availability and have shown that this particular brand of lithium carbonate is completely absorbed.

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[1] Eskalith capsules, Smith Kline and French Laboratories, Philadelphia, PA 19101.

[2] Diuril tablets, Merck Sharp and Dohme, West Point, PA 19486.

# *BOOKS*

## REVIEWS

**Clinical Pharmacy Sourcebook.** Key Articles from the American Journal of Hospital Pharmacy. Publishing Sciences Group, 162 Great Road, Acton, MA 01720, 1976. xvi + 396 pp. 22 × 28 cm. Price $20.00.

"Clinical Pharmacy Sourcebook" is, as its title indicates, a collection of carefully selected articles relating to clinical aspects of pharmacy service which have been published previously in the *American Journal of Hospital Pharmacy*. Thus, although not reflecting the entire universe of the clinically oriented pharmacy literature, the "Sourcebook" has tapped one of the most fertile sources of material on this important facet of pharmacy practice.

Stressing clinically oriented pharmacy practice rather than education, the "Sourcebook" is an excellent source of background information for pharmacy students, practicing pharmacists interested, but as yet not fully involved, in clinical practice, industrial representatives, and other health care professionals who desire to learn more about the contributions to direct patient care which can be offered by the clinically oriented pharmacist.

Readers of the "Sourcebook" will benefit also from its convenient organization. The book is divided into seven sections: Introduction; Clinical Pharmacy Services: Implementation and Administration; Clinical Pharmacy Services: The Hospitalized Patient; Clinical Pharmacy Services: The Ambulatory Patient; Clinical Pharmacy Services: Therapeutic Considerations; Clinical Pharmacy Services: Biopharmaceutics and Pharmacokinetics; and Clinical Pharmacy Services: Evaluation. This format does more than compartmentalize the material; it enables readers to select a specific area of interest such as therapeutics, develop the appropriate "mind set," and review easily a series of related articles in the area of interest selected.

In addition to the extensive number of references cited in each individual article, the "Sourcebook" contains a useful bibliography of approximately 160 selected references dealing with the clinical aspects of pharmacy practice and education. The book's index, which was computer generated from the International Pharmaceutical Abstracts Information