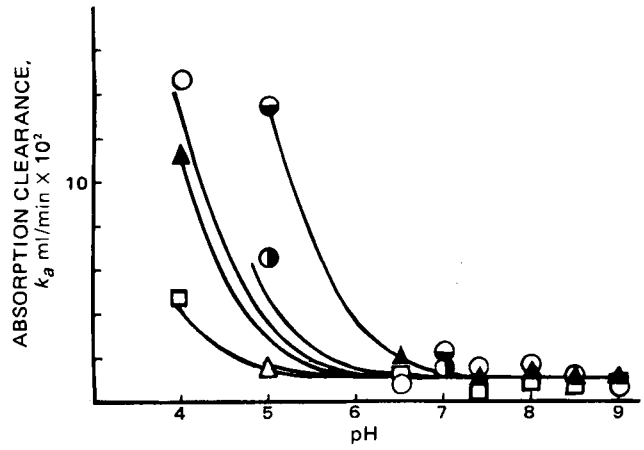

Figure 3—*Plots of the* in situ *rat intestinal absorption clearance,* k_{obs}, *of penicillins* versus *pH of the perfusion solution at 37°. The curves were generated from Eq. 5 with the corresponding parameters listed in Table II and from Ref. 4. Key:* ◒, *carindacillin (Ib);* ◑, *carfecillin (Ia);* ○, *dicloxacillin;* ▲, *propicillin;* □, *penicillin V; and* △, *carbenicillin (II). Data for dicloxacillin, propicillin, and penicillin V were taken from Ref. 4.*

for other antibiotics. The results indicate that the prodrugs, Ia and Ib, are sufficiently lipophilic to be absorbed rapidly from the GI tract by crossing the first barrier of the aqueous diffusion layer in front of the GI membrane surface and the second barrier of the lipid membrane.

The two prodrug chemical modifications of carbenicillin increase both the GI absorption rate and the acid-stability and exhibit sufficient chemical stability of the ester bond in the GI lumen. However, the results suggest that since the ester moieties of Ia and Ib are easily subject to the intestinal enzymatic metabolism, both ester prodrugs may liberate the poorly absorbable II as a result of nonspecific esterase action accompanied by absorption to reduce both bioavailabilities. After oral dosage in humans, 15–30% for Ia and 35–40% for Ib are recovered as II in urine compared with 75–100% after II intravenously (12). The relatively low recovery for I may be attributed to incomplete absorption and/or a first-pass effect. But II itself can not achieve a large urinary recovery after an oral dose.

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A Dissolution Anomaly Involving Ticrynafen in Simulated Intestinal Fluid without Enzyme

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Received March 2, 1981, from the *Research and Development Division, Smith, Kline & French Laboratories, Philadelphia, PA 19101.* Accepted for publication July 20, 1981.

Abstract □ Data are presented showing that the anomalous dissolution behavior of ticrynafen in simulated intestinal fluid without enzyme is due to the presence of potassium ions in the dissolution medium. Solubility studies indicate that an insoluble 1:1 complex is formed between ticrynafen and its potassium salt. This complex apparently creates an insoluble barrier that prevents complete dissolution of ticrynafen. To determine whether this might also occur in clinical use, a three-way cross-over study in 12 subjects was done. Data from this investigation show that concomitant administration of ticrynafen tablets and potassium in the form of a commercial supplement does not adversely affect bioavailability.

Keyphrases □ Ticrynafen—dissolution anomaly in simulated intestinal fluid without enzyme, potassium ions □ Potassium ions—complex with ticrynafen, dissolution anomaly in simulated intestinal fluid without enzyme □ Dissolution—anomaly, ticrynafen in simulated intestinal fluid without enzyme

Considerable effort has been devoted to the development of *in vitro* dissolution test methods that attempt to characterize the *in vitro* dissolution rate-controlled absorption of drugs administered in solid dosage forms. Unfortunately, the lack of understanding surrounding the many variables that can influence the *in vivo* dissolution, and possibly the subsequent absorption, make predictions based on *in vitro* data alone extremely difficult. The nature of the dissolution media can sometimes influence *in vitro* dissolution behavior dramatically and be misleading with regard to *in vivo* performance. The present study shows how the presence of potassium ions in simulated intestinal fluid without enzyme retarded drug dissolution without affecting the *in vivo* performance of ticrynafen[1].

EXPERIMENTAL

Materials—Ticrynafen[2], potassium ticrynafen[2], and 500-mg ticrynafen tablets[1] were obtained. All other chemicals were reagent grade and were used without further purification.

[1] 'Selacryn', Smith, Kline & French Laboratories.
[2] Smith, Kline & French Laboratories.

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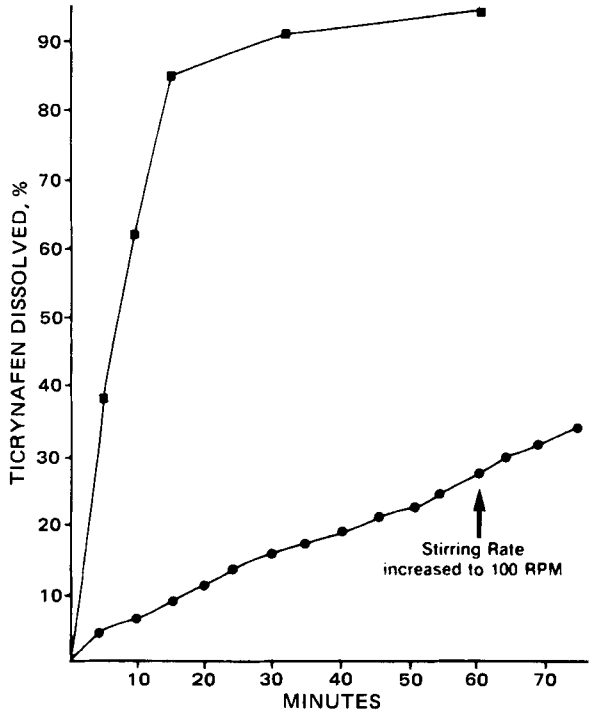

Figure 1—*Effect of stirring rate on the dissolution behavior of 500-mg ticrynafen tablets in simulated intestinal fluid without enzyme. Key: ●, 50 rpm; ■, 100 rpm.*

Dissolution Media—The following dissolution media were used in the dissolution studies: simulated intestinal fluid without enzyme USP (0.05 *M*), 0.05 *M* potassium phosphate buffer (pH 7.5), 0.05 *M* sodium phosphate buffer (pH 7.5), 0.05 *M* tromethamine buffer (pH 7.6). Buffers were freshly prepared prior to all dissolution studies.

Dissolution Methodology—The tablet dissolution profiles were determined in various buffer systems using Method II as described in the official compendia (1). The amount of drug dissolved with time was monitored by circulating the filtered dissolution media through a flow cell in a recording spectrophotometer[3] at 355 nm and returning it to the vessel. The ticrynafen absorbance *versus* time represents the dissolution profile of the tablet. The fractional amount of drug released as a function of time was determined by dividing the absorbance at any particular time by the absorbance after complete dissolution. A standard solution of ticrynafen (500 mg in 900 ml of dissolution medium) was utilized in the flow-cell apparatus to determine the absorbance when the tablet dissolution was complete.

Complexation Studies—A solubility method described previously (2) was utilized. Excess amounts of ticrynafen were placed in screw-capped glass vials. A 10-ml aliquot of various known concentrations of potassium ticrynafen was added to the vials. The samples were rotated overnight in a constant temperature bath at 25 ± 0.5°. An aliquot was removed from the vials, diluted with the appropriate solvent, and analyzed spectrophotometrically at 355 nm.

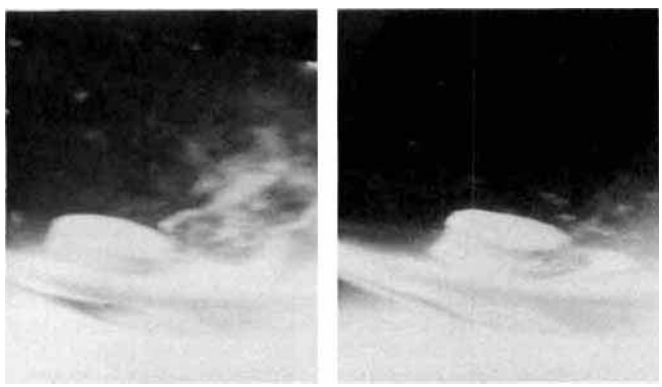

Figure 2—*Ticrynafen tablet (500 mg), initially and after 60 min in simulated intestinal fluid without enzyme.*

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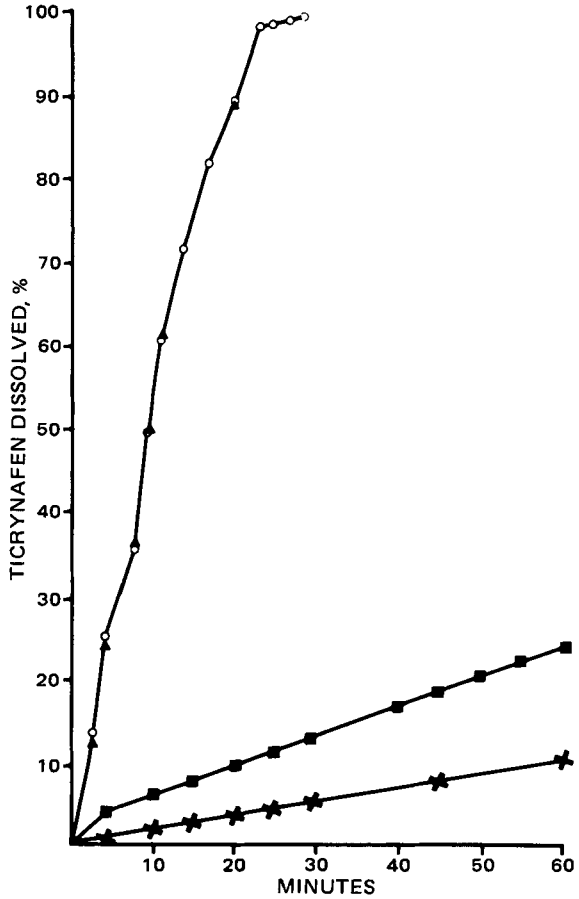

Figure 3—*Dissolution behavior of 500-mg ticrynafen tablets in simulated intestinal fluid without enzyme (■), 0.05 M potassium phosphate solution (×), 0.05 M sodium phosphate solution (○), and 0.05 M tromethamine solution (▲).*

RESULTS AND DISCUSSION

Dissolution Studies—Figure 1 shows the results of dissolution studies conducted with 500-mg ticrynafen tablets by USP Method II in simulated intestinal fluid without enzyme at 37° at 50 and 100 rpm, respectively. There appears to be a marked dependency on agitation. Physical observations during the dissolution test indicate that the tablet appeared to develop a crusty layer at the surface at 50 rpm. This effect is shown in Fig. 2. Since the ticrynafen tablets showed poor dissolution behavior at 50 rpm and developed the crust-like surface, it was thought that something in the system might be causing an interaction that resulted in poor dissolution. The effect also seemed dependent on agitation intensity, since complete tablet dissolution was achieved in 30 min at 100 rpm. In addition, increased agitation intensity had little, if any, effect on the dissolution behavior after the apparent interaction took place.

Additional dissolution studies were then conducted with several alternate buffer systems. Figure 3 shows the results of dissolution studies with 500-mg ticrynafen tablets in 0.05 *M* potassium phosphate, sodium phosphate, and tromethamine buffers and simulated intestinal fluid without enzyme, respectively. It is apparent that the presence of potassium ions in the dissolution media had a significant effect on the dissolution behavior of ticrynafen.

Since ticrynafen is usually administered to patients on concomitant potassium therapy, experiments were conducted to determine what effect

Table I—Summary of Blood Level and Urinary Excretion Data

Regimen	Blood Level *AUC*	Percentages Excreted
Tablet	173.67	30.20
Solution	170.16	30.49
Tablet with 20 meq potassium	165.83	31.55

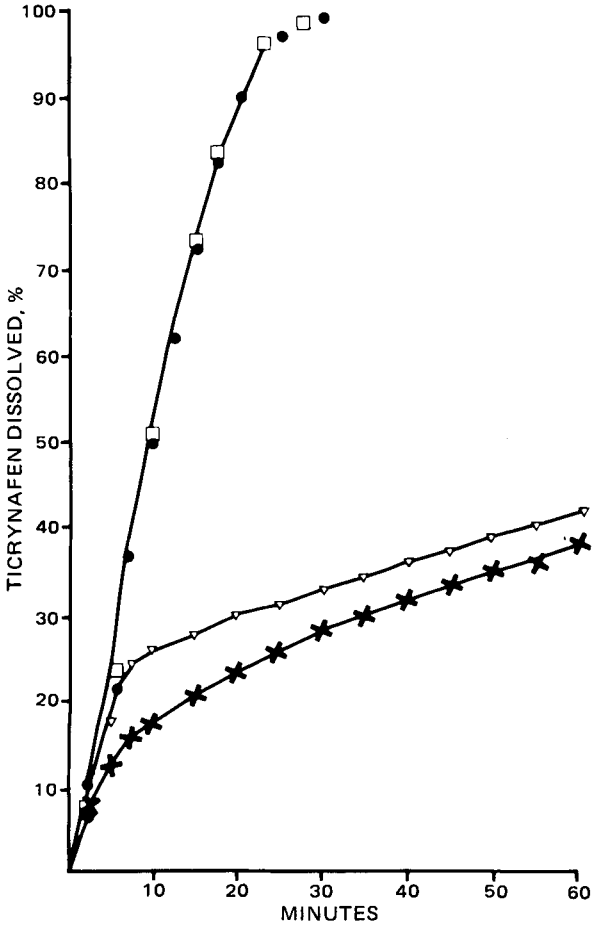

Figure 4—*Effect of the addition of potassium and sodium ions on the dissolution behavior of 500-mg ticrynafen tablets in 0.05* M *tromethamine solution (□), 0.05* M *tromethamine solution with 20 meq potassium added initially (×), 0.05* M *tromethamine solution with 20 meq potassium added after 5 min (▽), 0.05* M *tromethamine solution with 20 meq sodium added after 5 min (●).*

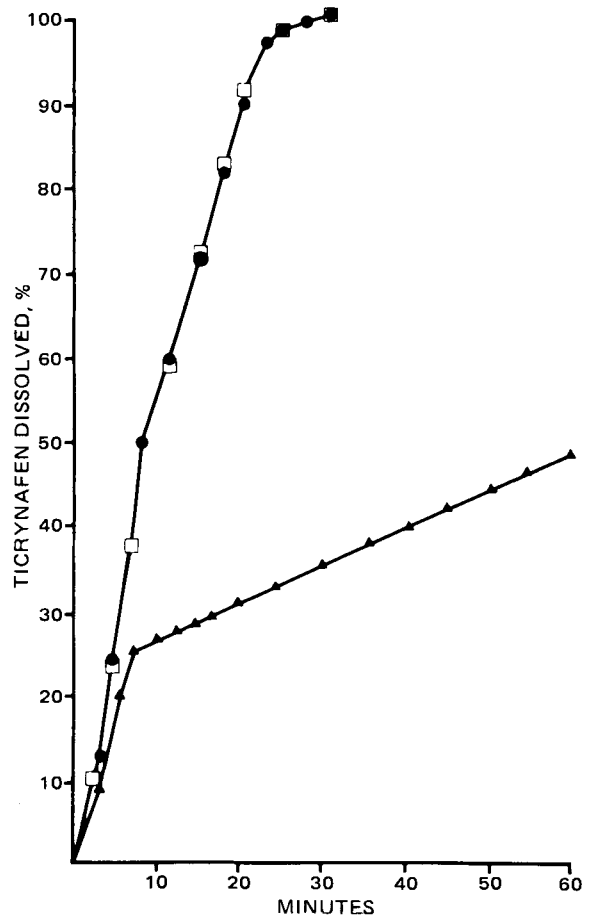

Figure 5—*Effect of the addition of potassium and sodium ions on the dissolution behavior of ticrynafen tablets (500 mg) in 0.05* M *sodium phosphate solution (●), 0.05* M *sodium phosphate solution with 20 meq potassium added after 5 min (▲), 0.05* M *sodium phosphate solution with 20 meq sodium added after 5 min (□).*

the addition of potassium to the tromethamine and sodium phosphate buffer solutions would have immediately and after 5 min on the dissolution behavior of ticrynafen. Sodium ions were also added in a separate experiment. Figures 4 and 5 show the results of these studies. The data indicate that the addition of 20 meq of potassium has a significant effect on the dissolution behavior of ticrynafen and appears to be more pronounced when the potassium ions are added immediately. The addition of 20 meq of sodium has no apparent effect.

To determine if this physicochemical phenomenon was reversible, dissolution studies were done in which 500-mg ticrynafen tablets were placed in 0.05 *M* potassium phosphate buffer. After 15 min the buffer solution was replaced carefully with 0.05 *M* tromethamine buffer solution and the dissolution test was continued for 1 hr. The results of these studies are shown in Fig. 6. It is apparent that this effect is not completely reversible. After changing the medium, dissolution did not proceed at the rate observed in tromethamine buffer. Figure 6 also includes a dissolution study in which the tablet was accidentally disturbed during the transfer of dissolution medium. This apparently created a fresh surface of drug which resulted in increased dissolution. In the case where the tablet was not disturbed the effect was less dramatic. However, in both cases the dissolution of the tablet after the exchange of media did not approach its dissolution in 0.05 *M* tromethamine buffer.

Complexation Studies—Previous reports showed that organic acids can interact with their alkali salts to form soluble and insoluble complex species (3, 4). Since the presence of potassium ions in the dissolution media had such a dramatic effect on the dissolution behavior of ticrynafen it was thought that complex formation might be responsible. Solubility studies were conducted to detect this interaction (Fig. 7). Initially, solubility increased which suggested an interaction had taken place. As more complex formed, the system became saturated with respect to the complex, and precipitated from solution. This is shown by the plateau region in Fig. 7. The pH of the system in this plateau region remained constant even with the continued addition of potassium ticrynafen solution. Since the slope of the initial solubility curve is 2, a complex having a stoichiometry of 1:1 is formed. If no complex was formed this initial slope should be 1, since the appearance of ticrynafen in solution was followed spectrophotometrically.

Samples of the complex were isolated from the saturated solution and analyzed for potassium by atomic absorption spectroscopy. A potassium content of 4.54% was found, which compares favorably with the theoretical potassium content of 4.5% calculated on the basis of a 1:1 complex.

The solubility increases at ~0.01 *M* potassium ticrynafen concentration indicating that the complex is probably soluble in an excess of the potassium ticrynafen solution. This apparently explains the dissolution behavior. During the dissolution of ticrynafen in systems containing potassium ions, a conversion of the free acid to the potassium salt takes place. Apparently, under the conditions of the study, the complex forms at 50 rpm more readily, creating an insoluble barrier which further retards dissolution. However, at 100 rpm the conditions are such that the optimum concentration for the formation of the complex is exceeded rapidly, due to the rapid dissolution of the drug at this agitation intensity.

Bioavailability Studies—Bioavailability studies were conducted to determine the effect of concomitant potassium therapy on the availability of ticrynafen from 500-mg ticrynafen tablets. A three-way cross-over study with a 1-week wash-out period between regimens was conducted in 12 normal, randomly selected adults. The following regimens were tested: (*a*) a 500-mg ticrynafen tablet, (*b*) a solution containing 500 mg of ticrynafen, (*c*) a 500-mg ticrynafen tablet with 20 meq of potassium administered simultaneously (15 ml of a 10% potassium elixir). Blood samples were collected at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hr after the administered dose. Urine was collected for 24 hr before and 24 after dosing. Fractional urine collections after administration of the regimens were obtained at 0–4, 4–6, 8–12, and 12–24 hr. The concentration of ticrynafen in plasma and urine samples was determined by an automated high-

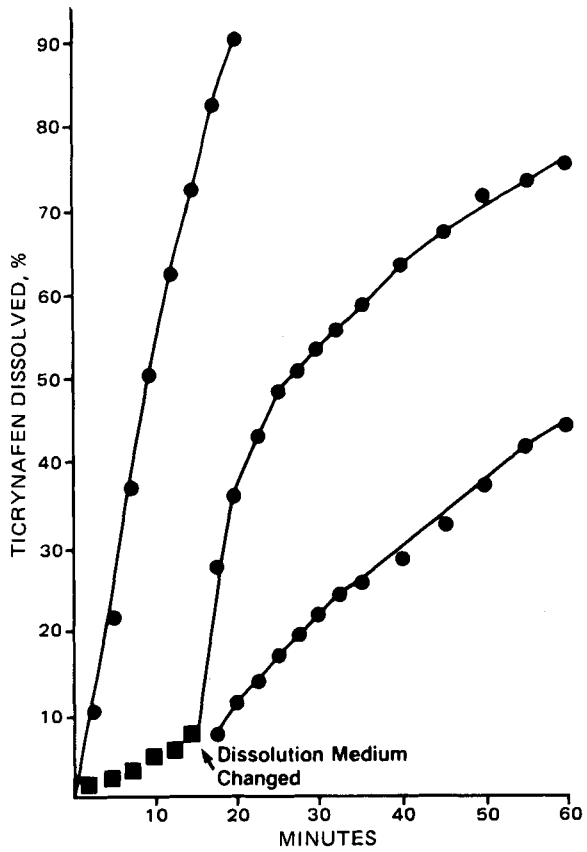

Figure 6—*Effect of media exchange on the dissolution behavior of ticrynafen tablets (500 mg) in 0.05* M *tromethamine solution (●), 0.05 M potassium phosphate solution for 15 min then replaced with 0.05* M *tromethamine solution (■).*

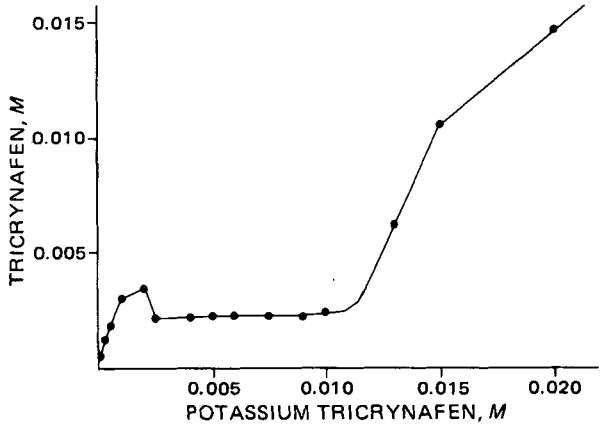

Figure 7—*Effect of potassium ticrynafen on the equilibrium solubility of ticrynafen.*

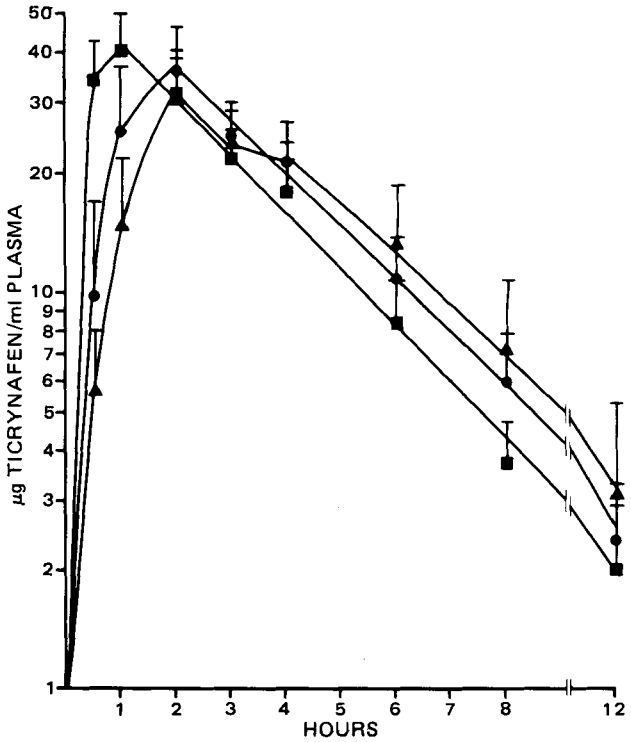

Figure 8—*Mean plasma ticrynafen levels* ± SD *after administration of 500-mg tablet (●), 500-mg solution (■), 500-mg a tablet with 20 meq potassium (▲).*

pressure liquid chromatographic procedure (5). The extraction and analysis of plasma and urine were accomplished in a completely automated fashion using an automatic HPLC system[4]. Figure 8 illustrates the blood level profiles obtained for the various dosage regimens. The area under the blood level curves and the urinary excretion were used as a measure of bioavailability (Table 1). There were no statistically significant differences between the regimen means for the area under the blood level curves or the percentage excreted in the urine when a t test was applied at the 95% confidence interval. Thus, the concomitant use of potassium supplements should not affect the bioavailability of ticrynafen in clinical use.

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