Solubility and Dissolution Rate Studies of Ergotamine Tartrate

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Received January 25, 1980, from the *School of Pharmaceutics, Victorian College of Pharmacy, Parkville, Victoria, Australia 3052.* Accepted for publication February 27, 1980.

Abstract ☐ The solubility of ergotamine tartrate in aqueous solutions of tartaric acid, citric acid, hydrochloric acid, and caffeine and the dissolution rate of ergotamine tartrate in aqueous mixtures containing hydrochloric acid, caffeine, citric acid, or sodium acetate were studied. The Noyes–Whitney model of dissolution is useful for predicting the dissolution rate of ergotamine tartrate in most of the dissolution media. The relative slowness with which ergotamine chloride (a substance with low water solubility) precipitated when ergotamine tartrate was dissolved in 0.1 *M* HCl resulted in the solid dissolving faster in this medium than was predicted using the Noyes–Whitney equation.

Keyphrases ☐ Ergotamine tartrate—solubility and dissolution rate ☐ Analgesics—ergotamine tartrate, solubility and dissolution rate ☐ Solubility—ergotamine tartrate, various dissolution media ☐ Dissolution rates—ergotamine tartrate, various dissolution media

Relief of migraine headaches by the ergot alkaloid ergotamine depends on its rapid entrance into the systemic circulation during the initial phase of the migraine attack (1). Ergotamine has very low water solubility (2), and its more soluble salts, especially ergotamine tartrate (ergotamine:tartaric acid, 2:1), are used in injections and in solid dosage forms from which rapid drug release is desirable (3).

Although ergotamine tartrate, with a solubility of 1:500 in water (2), is more soluble in water than ergotamine, some confusion exists about the nature of its aqueous solutions. For example, it was stated that ergotamine tartrate is soluble in water but that the addition of tartaric acid often is necessary to maintain a clear solution (4). The present studies concern the solubility of ergotamine in aqueous solutions of tartaric acid, citric acid, hydrochloric acid, and caffeine and the dissolution rate of ergotamine tartrate in several aqueous mixtures. Caffeine was included in some solutions because it is a common ingredient in many dosage forms of ergotamine and it has been postulated that caffeine forms one or more molecular complexes with ergotamine (5).

EXPERIMENTAL

Solubility Studies—Solutions of caffeine, citric acid, and tartaric acid were prepared in the concentration ranges of 0–0.025, 0–0.25, and 0–0.25 *M*, respectively. The pH values of these solutions were adjusted with sulfuric acid, hydrochloric acid, or sodium hydroxide (Table I).

Constant amounts of ergotamine tartrate, in excess of its solubility, were added to screw-capped vials containing a fixed volume of dissolution medium. The vials were sealed and shaken in a water bath at 25.0 ± 0.1°. Preliminary studies were conducted to determine the time required for the solutions to reach equilibrium.

The ergotamine concentration in each equilibrated solution was determined by filtering the contents of the screw-capped vials through a 0.22-μm membrane filter, diluting the filtrate with 1.0% (w/v) tartaric acid solution, and measuring the absorbance of these solutions at 317 nm against an appropriately diluted dissolution medium. Absorbance values were converted to ergotamine concentrations using a Beer's law plot. The Beer's law plot was constructed over the ergotamine concentration range of 0–1.52 × 10^{-4} *M* and was found to fit $y = 7318x$ ($r = 0.999$), where y is the absorbance and x is the molar concentration of ergotamine.

The amounts of ergotamine tartrate, the volumes of the dissolution media, and the shaking times for each solubility experiment are shown in Table I.

Analysis of Solids—The solid phases remaining in several solubility experiments were collected and dried at 100°. The percentage by weight of ergotamine in the solid phase was determined by dissolving a known amount of the solid and measuring its absorbance at 317 nm. The concentration of ergotamine in the solution was determined from a standard curve, thus allowing the percentage composition of ergotamine in the solid phase to be calculated.

Dissolution Studies—The apparatus used in the dissolution studies was a slight modification of the assembly described in USP XIX. A flow inducer[1] was used to pump the dissolution medium into a flow-through cell mounted in a spectrophotometer[2] and back into the dissolution vessel. The absorbance of ergotamine in the circulating dissolution medium was measured at 317 nm, and a dissolution curve was constructed by plotting ergotamine concentration *versus* time.

The dissolution tests were conducted on 100-mg disks of ergotamine tartrate, manufactured by compression at a force of 5 tons in a hydraulic press. The dissolution medium (1000 ml) was maintained at 25.0 ± 0.1°, and the basket of the dissolution apparatus was rotated at 100 rpm.

The compositions of the dissolution media (Table II) were designed to determine the influence of caffeine and citric acid on the dissolution rate of ergotamine in simulated gastric fluid (0.1 *M* HCl) and at the approximate pH value of the region where the stomach empties its contents into the duodenum (pH 5.0, 0.1 *M* sodium acetate–acetic acid buffer).

RESULTS AND DISCUSSION

Ergotamine Solubility in Aqueous Tartaric Acid Solutions—The phase solubility diagram for ergotamine in aqueous tartaric acid solutions is shown in Fig. 1. The points were calculated from the results of experiments in which water or the tartaric acid solutions were saturated with ergotamine tartrate. The pH values of the various solutions are indicated in Fig. 1. The solution that was prepared by saturating water with ergotamine tartrate [$(EH)_2T$] had a pH value of <5.2, which is the calculated pH value of such a solution [the solution contained 3.2 × 10^{-3} *M* ergotamine plus ergotamine cation; the pKa value of ergotamine cation is 6.4 (6), and the pKa values for tartaric acid are 2.93 and 4.23 (2)]. This point will be discussed more fully later, but it is believed to arise because the ergotamine tartrate sample was contaminated with tartaric acid or ergotamine acid tartrate (EHTH).

The fact that ergotamine cation has pKa value of 6.4 leads to the conclusion that ergotamine is essentially fully protonated between pH 3 and 1.86, so changes in solubility that accompany changes in tartaric acid concentration cannot be accounted for by changes in the degree of ionization of ergotamine.

The solid phase in the presence of 0.25 *M* added tartaric acid contained 80.3% ergotamine and 19.7% tartaric acid. Since this is a 1:1 molar ratio of ergotamine and tartaric acid, the compound is postulated to be ergotamine acid tartrate. The solid phase in the presence of 0.025 *M* added tartaric acid had an ergotamine to tartaric acid ratio of 1.4:1 and most likely was a mixture of EHTH and ergotamine tartrate [$(EH)_2T$].

These observations and the phase solubility diagram can be accounted for on the basis that the reactions shown in Schemes I–IV occur in saturated aqueous solutions of ergotamine tartrate. In Schemes I–IV, EH^+ is the ergotamine cation; TH_2, TH^-, and T^{2-} are tartaric acid, acid tartrate ion, and tartrate ion, respectively; K_s^1 and K_s^2 are the solubility products of $(EH)_2T$ and EHTH, respectively; and K_a^1 (1.04 × 10^{-3}) and K_a^2 (4.55 × 10^{-5}) are the acid dissociation constants of tartaric acid (2).

[1] Watson-Marlow Ltd.
[2] Perkin-Elmer 402 UV–visible spectrophotometer.

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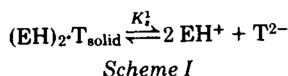
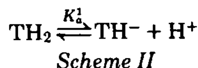
Table I—Composition of the Dissolution Media and Experimental Parameters Used in the Solubility Studies

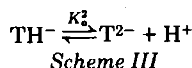
Medium	Dissolution Medium pH	Composition of Dissolution Medium	Amount of Ergotamine Tartrate, mg	Volume of Dissolution Medium, ml	Shaking Time, hr
1	0.3	0–0.025 *M* caffeine and 0.5 *M* sulfuric acid	100	20	24
2	0.5	0–0.025 *M* caffeine and 0.37 *M* HCl	100	20	24
3	1.0	0–0.025 *M* caffeine and 0.1 *M* HCl	100	20	48
4	1.4	0–0.025 *M* caffeine and 0.037 *M* HCl	100	20	24
5	2.0	0–0.025 *M* caffeine and 0.01 *M* HCl	100	20	48
6	Not controlled	0–0.25 *M* aqueous citric acid solution	250	10	48
7	5.0	0–0.25 *M* aqueous citric acid–sodium hydroxide solution	50	10	48
8	1.0	0–0.25 *M* citric acid and 0.1 *M* HCl	100	20	48
9	1.0	0–0.25 *M* citric acid, 0.025 *M* caffeine, and 0.1 *M* HCl	100	20	48
10	Not controlled	0–0.25 *M* aqueous tartaric acid solution	200	10	48



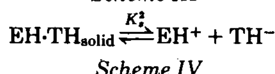
Scheme I



Scheme II



Scheme III



Scheme IV

The observation that the solid phase in the presence of 0.025 *M* tartaric acid was a mixture of ergotamine tartrate and ergotamine acid tartrate suggests that the solid phase throughout the ascending portion of the phase solubility diagram, *i.e.*, from 0 to 0.05 *M* added tartaric acid, was a mixture of $(EH)_2T$ and EHTH and that the equilibrium reactions in Schemes I and IV were established. Hence, throughout this region, the relationship:

$$\frac{K_s^1}{K_s^2} = \frac{[EH^+]K_a^2}{[H^+]} \quad \text{(Eq. 1)}$$

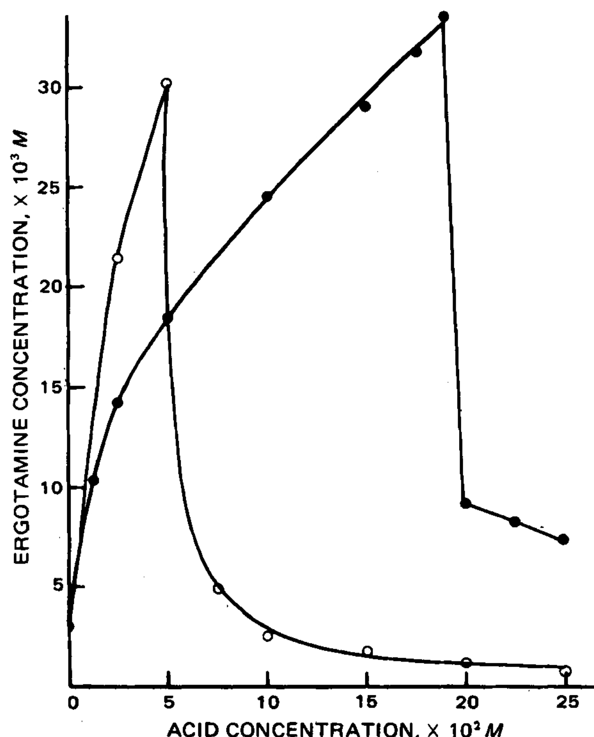


Figure 1—*Effect of the tartaric acid concentration* (○) *and citric acid concentration* (●) *on the solubility of ergotamine tartrate in water. The concentrations of tartaric acid added resulted in various pH values of equilibrated solution: 0* M, *3.0; 0.025* M, *2.33; 0.05* M, *2.15; 0.075* M, *2.10; 0.10* M, *2.04; 0.15* M, *1.98; 0.20* M, *1.92; and 0.25* M, *1.86.*

should apply. Substitution of measured values of $[EH^+]$ and $[H^+]$ in Eq. 1 led to a value of $2.0 \pm 0.1 \times 10^{-4}$ *M* for K_s^1/K_s^2. The solid phase in the presence of 0.25 *M* added tartaric acid was ergotamine acid tartrate. Hence, under these conditions, it is evident that the equilibrium reactions in Schemes II–IV are the only ones operating. Treatment of the data in this region resulted in a value of 2.1×10^{-5} M^2 for K_s^2. Subsequent solution of Eq. 1 gave a value of 4.2×10^{-9} M^3 for K_s^1. Hence, the phase solubility diagram in Fig. 1 may be accounted for by the described postulates and can be quantitated by using values of 4.2×10^{-9} M^3 and 2.1×10^{-5} M^2 for the equilibrium constants K_s^1 and K_s^2 at 25°, respectively.

The presence of EHTH in the EH_2T sample that was obtained commercially could account for the fact that its saturated solution in water had a pH value of 3.0 rather than 5.2 as expected. The analytical results found for this material were: C, 62.11; H, 5.83; N, 10.44; O, 21.52. The formula for $(EH)_2T$ ($C_{70}H_{76}N_{10}O_{16}$) requires: C, 64.01; H, 5.83; N, 10.66; O, 19.49. Therefore, the analytical results are consistent with it containing 50% $(EH)_2T$ and 50% EH·TH (C, 62.36; H, 5.74; N, 10.12; O, 21.77).

If this postulate is correct, then the determinations of ergotamine concentrations made in this study are probably in error by 5% because the Beer's law plots from which concentrations were calculated were constructed on the basis that 1 mole of ergotamine tartrate yielded 2 moles of ergotamine cation. In fact, whereas 1 g of ergotamine tartrate yields 1.52×10^{-3} mole of ergotamine cation, 1 g of a 50:50 mixture of ergotamine tartrate and ergotamine acid tartrate yields 1.45×10^{-3} mole of ergotamine.

Ergotamine Tartrate Solubility in Aqueous Citric Acid Solutions—The phase solubility diagram obtained by saturation of citric acid solutions with ergotamine tartrate is included in Fig. 1. The solid phase in the presence of 0.25 *M* citric acid was a 1:1 mixture of citric acid and ergotamine, presumably the monoergotamine salt of citric acid.

The pH values of solutions in this experiment were not controlled and ranged downward from 3.0. This system was not analyzed further because of its complexity, but it is reasonable to conclude that equilibria similar to those established in the tartaric acid system were in existence as well as others involving the various possible salts of citric acid.

The phase solubility diagram obtained when ergotamine tartrate was added to pH 5.0 citric acid–sodium hydroxide buffers is shown in Fig. 2.

Table II—Dissolution Rates of 100-mg Ergotamine Tartrate Disks in Various Dissolution Media

Composition of Dissolution Medium	pH Value	Gradient of Initial Portion of Dissolution Curve, absorbance units/min × 10⁴
0.1 *M* HCl	1.0	35.3 ± 10.5
0.025 *M* caffeine and 0.1 *M* HCl	1.0	288.0 ± 93.1
0.15 *M* citric acid and 0.1 *M* HCl	1.0	83.0 ± 34.1
0.025 *M* caffeine, 0.15 *M* citric acid, and 0.1 *M* HCl	1.0	246.3 ± 99.2
0.1 *M* sodium acetate–acetic acid buffer (acetate buffer)	5.0	37.0 ± 19.1
0.025 *M* caffeine and acetate buffer	5.0	150.3 ± 49.8
0.15 *M* citric acid–sodium hydroxide in acetate buffer	5.0	6.7 ± 1.9
0.025 *M* caffeine and 0.15 *M* citric acid–sodium hydroxide in acetate buffer	5.0	18.3 ± 2.1

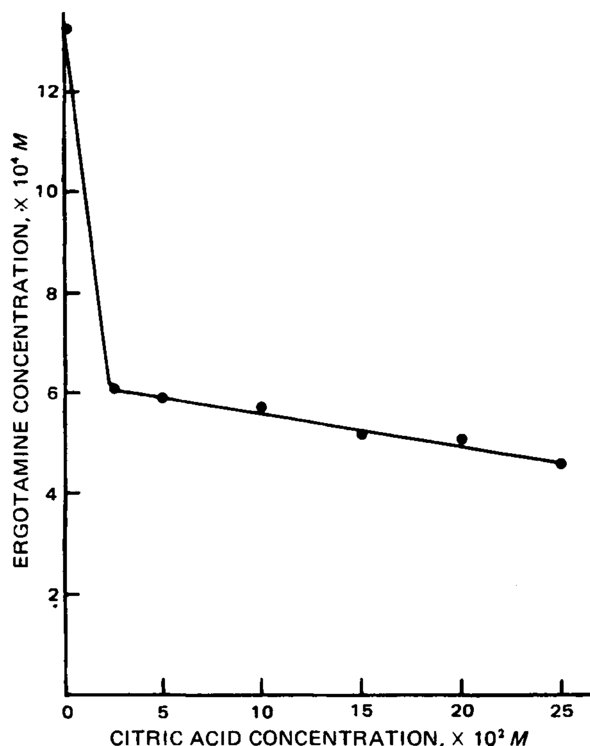
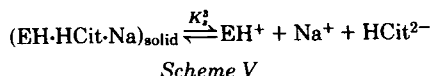


Figure 2—*Solubility of ergotamine tartrate in solutions of citric acid buffered to pH 5.0 with sodium hydroxide.*

In this case, increases in the total citrate concentration caused the ergotamine concentration in solution to decrease. The solid phase in the presence of 0.25 *M* added citric acid contained 72.3% ergotamine. This value is consistent with the solid phase being essentially the monosodium, monoergotamine salt of diionized citric acid, which contains 73.09% ergotamine (EH·HCit·Na). The equilibrium reaction under these conditions is:



$$(\text{EH·HCit·Na})_{\text{solid}} \overset{K_s^3}{\rightleftharpoons} \text{EH}^+ + \text{Na}^+ + \text{HCit}^{2-}$$

Scheme V

The decrease in ergotamine concentration in solution that occurred as the sodium citrate concentration was increased resulted from precipitation of EH·HCit·Na by a common-ion effect.

Ergotamine Tartrate Solubility in Aqueous Hydrochloric Acid—The solubilities of ergotamine tartrate in aqueous hydrochloric acid solutions are summarized in Table III. The solid phases were not analyzed[3], but it is postulated that they contained ergotamine chloride. It is known from the pKa value of ergotamine cation (6.4) that the ionic nature of ergotamine does not change appreciably as the pH is lowered from 3.0 (10^{-3} *M* HCl) to ~1.0 (0.1 *M* HCl). Hence, increasing chloride-ion concentrations probably caused precipitation of ergotamine chloride by a common-ion effect. This conclusion is supported by the fact that the product of the concentrations of ergotamine cation [EH^+] and chloride ion in solution was essentially constant (Table III), *i.e.*, it was the solubility product of ergotamine chloride. The slight drift in values could be caused by the change in ionic strength that occurs when the chloride-ion concentration varies by a factor of >100.

The chloride-ion concentrations in the stomach and duodenum are ~0.14 *M* (5 mg/ml) and 0.08 *M* (2.6–3.6 mg/ml), respectively (7). Hence, the precipitation of ergotamine chloride in the GI tract may lower the bioavailability of orally administered ergotamine salts.

Table III—Solubility of Ergotamine in Aqueous Hydrochloric Acid

[HCl], *M*	$10^4[\text{EH}^+]$, *M*	$[\text{Cl}^-]^a$, *M*	$K_{SP} = [\text{EH}^+][\text{Cl}^-]$, M^2
0.370	0.58	0.362	2.1×10^{-5}
0.100	0.64	0.093	5.9×10^{-6}
0.037	1.77	0.030	5.2×10^{-6}
0.010	7.76	0.003_2	2.5×10^{-6}

[a] Calculated on basis that the solid phase is ergotamine chloride.

[3] A UV spectrum and flame test were consistent with this conclusion.

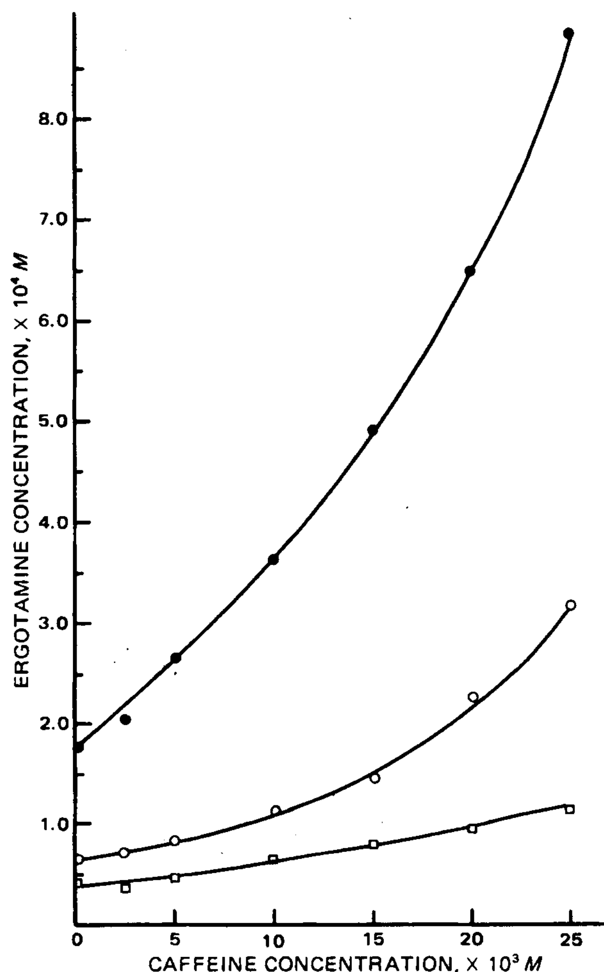


Figure 3—*Effect of caffeine concentration on the solubility of ergotamine in 0.370* M *HCl (□), 0.100* M *HCl (○), and 0.037* M *HCl (●).*

Zoglio *et al.* (5) determined the solubility of ergotamine tartrate in 0.1 *M* HCl at 30.0° to be ~5.3×10^{-3} *M* ergotamine. This figure is substantially larger than the value of 8.1×10^{-5} *M* calculated in this study under identical conditions. No explanation for this difference can be offered.

Ergotamine Tartrate Solubility in Caffeine Solutions—The phase solubility diagrams that were obtained by saturation of caffeine solutions in aqueous hydrochloric acid with ergotamine tartrate are shown in Figs. 3 and 4. The influence of caffeine on ergotamine tartrate solubility was qualitatively similar to that obtained by Zoglio *et al.* (5) and may be attributed to complex formation between caffeine and ergotamine. The fact that the ergotamine–caffeine phase solubility diagrams are not straight lines suggests that complexes containing more than one caffeine molecule were formed (8).

Dissolution Studies—The dissolution rates of ergotamine from 100-mg ergotamine tartrate disks in various solvents are shown in Table II. The dissolution rates in 0.1 *M* HCl were increased 6.5 times when 0.025 *M* caffeine was included and 2.4 times when 0.15 *M* citric acid was included. The rate was increased seven times in the presence of 0.025 *M* caffeine and 0.15 *M* citric acid. The phase solubility studies indicated that ergotamine tartrate solubility (expressed as ergotamine solubility) in 0.1 *M* HCl was increased six times by 0.025 *M* caffeine and six times by citric acid. Hence, these results were approximately consistent with the Noyes–Whitney model for dissolution (9), which states that the dissolution rate of a solid is proportional to its solubility in dilute solutions.

It is surprising that the dissolution rate of ergotamine in a pH 5.0 acetate buffer was essentially the same as that in 0.1 *M* HCl, whereas its solubility was 20 times greater in the former solvent. A likely explanation is that precipitation of ergotamine chloride, the event that depresses ergotamine solubility in hydrochloric acid solutions, does not occur to an appreciable extent within the diffusion layer. The kinetics of this event apparently are slow with respect to the time taken for a molecule to dif-

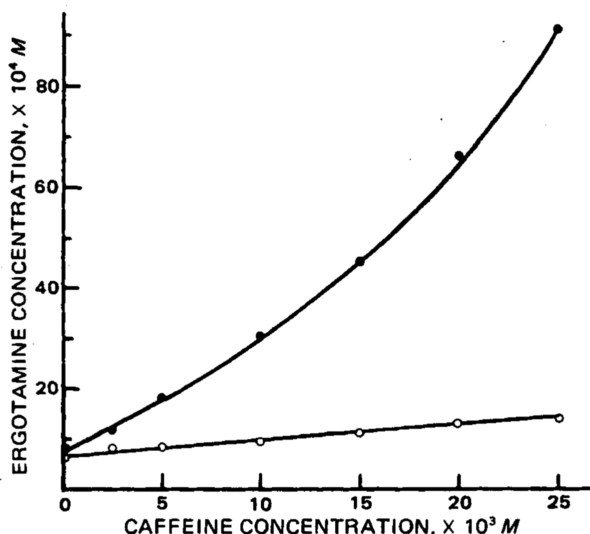


Figure 4—*Solubilizing effect of caffeine on ergotamine tartrate in 0.01* M *HCl* (●) *and 0.50* M *sulfuric acid* (○).

fuse from the solid–liquid interface into the bulk of the solution.

The inclusion of 0.025 *M* caffeine in a pH 5 acetate buffer increased the dissolution rate of ergotamine tartrate four times, whereas the inclusion of 0.15 *M* citric acid depressed the rate by a factor of five. The inclusion of 0.15 *M* citric acid in the acetate buffer that contained 0.025 *M* caffeine reduced the rate by a factor of eight.

The rate-enhancing effect of caffeine on ergotamine dissolution at pH 5.0 is consistent with the formation of a soluble molecular complex at this pH as well as at pH 1.0. These studies provided evidence of complex formation at pH 1.0, and Zoglio *et al.* (5) demonstrated complex formation at pH 6.65.

The results in Fig. 2 show that citric acid depressed ergotamine solubility in a pH 5 sodium acetate buffer by a factor of 2.4. Hence, the depressing effect of citric acid on the dissolution rate of ergotamine in a pH 5 buffer is consistent with predictions based on the Noyes–Whitney model.

CONCLUSIONS

1. Chloride ions, a common constituent of the contents of the stomach and duodenum, significantly reduce the concentration of ergotamine in solution by forming ergotamine chloride, a substance with a solubility product of $\sim 5 \times 10^{-6}\ M^2$.
2. The dissolution rate of ergotamine tartrate in water is not depressed appreciably by chloride ions because the precipitation rate of ergotamine chloride apparently is slow compared to the dissolution rate.
3. Protonation of the diionized tartrate anion of ergotamine tartrate by the addition of small amounts of citric acid or tartaric acid increases the solubility of ergotamine. Large amounts of these acids result in the precipitation of 1:1 salts of ergotamine and the acid monoanions. Sodium citrate depresses the solubility of ergotamine.
4. The Noyes–Whitney model for dissolution accounts for the rate-enhancing effect of caffeine and citric acid on ergotamine dissolution at pH 1.0 and the rate-depressing effect of citric acid at pH 5.0.

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ACKNOWLEDGMENTS

Supported by a grant from the Nicholas Drug Research Consortium.

Wall-Coated Open Tubular Column Coupled with Nitrogen-Selective Detector for Routine GLC Determination of Diazepam, Meprobamate, Phenylbutazone, and Thioridazine in Serum

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Received March 28, 1979, from the *Laboratory of Pharmacology, Medical School, Laboratory of Functional Explorations B, University Hospital Center of Caen, 14000 Caen, France.* Accepted for publication February 26, 1980.

Abstract ☐ The selectivity and sensitivity provided by a wall-coated open tubular column coupled with a nitrogen-selective detector allowed rapid, accurate determination of diazepam, meprobamate, phenylbutazone, and thioridazine in serum in the same chromatographic system using 100–200 μl of sample.

Keyphrases ☐ Diazepam—GLC determination in serum, wall-coated open tubular column coupled with nitrogen-selective detector ☐ Meprobamate—GLC determination in serum, wall-coated open tubular column coupled with nitrogen-selective detector ☐ Phenylbutazone—GLC determination in serum, wall-coated open tubular column coupled with nitrogen-selective detector ☐ Thioridazine—GLC determination in serum, wall-coated open tubular column coupled with nitrogen-selective detector ☐ GLC—analysis, diazepam, meprobamate, phenylbutazone, and thioridazine in serum, wall-coated open tubular column coupled with nitrogen-selective detector

Various columns and detectors have been used in the GLC determination of diazepam (I) (1–7), meprobamate (II) (8, 9), phenylbutazone (III) (10–14), and thioridazine (IV) (15–17) in serum. Packed columns were used in all of the methods and were coupled to a ^{63}Ni-electron-capture detector (1–5, 7, 14), a flame-ionization detector (6, 8–13,

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