Complexes of Ergot Alkaloids and Derivatives V: Interaction of Methysergide Maleate and Caffeine in Aqueous Solution

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Abstract □ Evidence of complex formation between methysergide maleate and caffeine is presented, utilizing solubility and vapor pressure osmometer information. The effect of this interaction on the rate of dissolution and partitioning-rate behavior of methysergide maleate has been measured. The absorption consequences of this interaction as implied from the *in vitro* studies are presented.

Keyphrases □ Methysergide maleate, caffeine complexes—interactions in aqueous solutions, effect on dissolution, partition rates □ Vapor pressure osmometry—complex formation data, methysergide maleate, caffeine □ Ergot alkaloids, derivatives—complexes, methysergide, caffeine

The successful utilization of complexing phenomena to enhance the absorption of proteinaceous ergot alkaloids (1, 2) prompted an investigation into the possible interaction of a synthetic nonproteinaceous ergot alkaloid with caffeine. The drug, methysergide maleate,[1] (+)-9,10-didehydro-*N*-[1-(hydroxymethyl)propyl]-1,6-dimethylergoline-8β-carboxamide maleate, was studied with caffeine in aqueous media, utilizing changes in apparent solubility and vapor pressure osmometry to detect complexation. After establishing an interaction, the pH dependency of the interaction was examined. Studies of the consequence of the interaction on *in vitro* dissolution and partition rates were undertaken to gain some insight into potential *in vivo* absorption effects.

EXPERIMENTAL

Materials—Methysergide maleate[2] (mol. wt. 469.54) showed only trace contaminants when subjected to TLC. Anhydrous caffeine powder USP,[3] m.p. 238°, was utilized in this study.

Reagent grade chloroform[4] was employed in the partitioning-rate studies. A pH 6.65 buffer was made by dissolving 13.6 g. KH_2PO_4 in 500 ml. water, adjusting the pH with concentrated KOH, and diluting to 1 l. (ionic strength 0.2).

The pH measurements were made on a Metrohm pH meter, and spectrophotometric data were obtained from a Cary model 14 spectrophotometer.

Solubility Studies—Methysergide maleate, 1.5 g., was placed in watertight, amber, screw-capped vials (50 ml.) containing 10 ml. of either distilled water, 0.1 *M* pH 6.65 phosphate buffer, or 0.1 *N* HCl, and varying quantities of anhydrous powdered caffeine were added. The vials were clamped onto the edge of metal disks (15-cm. diameter) mounted on a motor-driven shaft and rotated vertically at 6 r.p.m. in a constant-temperature bath, 30 ± 0.1°. After 24 hr., samples were taken using pipets with filters attached and were analyzed for methysergide maleate by UV spectrophotometry (325 mμ).

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[2] Sandoz A.-G., Basel, Switzerland.
[3] Chas. Pfizer Co.
[4] Mallinckrodt.

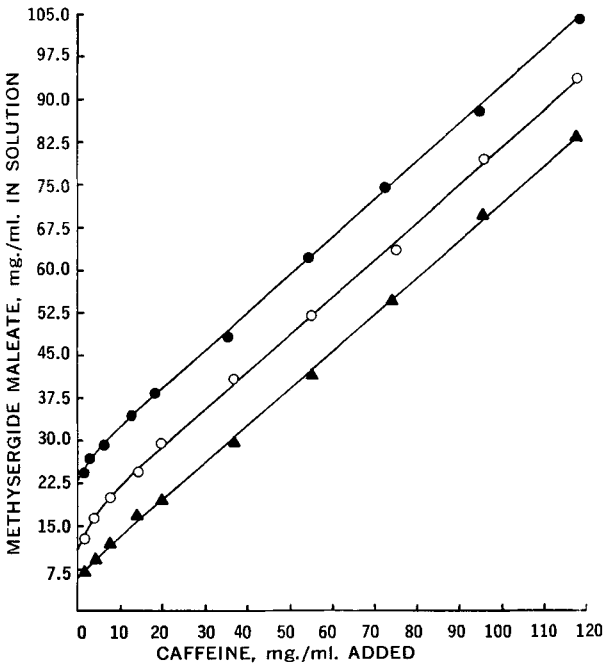

Figure 1—*Apparent solubility changes for methysergide maleate as a function of added caffeine. Key:* ●, *0.1* N *HCl, pH = 1.25;* ○, *distilled water; and* ▲, *0.1* M *phosphate buffer, pH = 6.65.*

Vapor Pressure Osmometry—A model 301A Mecrolab (Hewlett-Packard) vapor pressure osmometer was employed in these studies. The instrument was calibrated using solutions of raffinose in distilled water. Forty-eight hours was allowed for thermal equilibration before measurements were taken. Samples were inserted into the chamber containing the thermistor beads 3 hr. prior to reading. Solutions were prepared from the same lot of deionized distilled water. The reservoir of water used in the measuring chamber was also taken from this lot and changed after each series of five readings with subsequent reequilibration of the instrument.

Partitioning Studies—A solution was prepared by placing methysergide maleate, 100 mg., in 950 ml. of pH 6.65 phosphate buffer, stirring magnetically for 30 min. to 1 hr., and filtering (Whatman No. 1 filter paper) into a flask immersed in a water bath maintained at 30°. Finally, pH 6.65 buffer was added to make 1 l. of solution. Five hundred milliliters of this solution was kept, and 500 ml. had caffeine (5 g.) added to it.

Fifteen milliliters of the freshly prepared aqueous phase—either with or without xanthine—was added carefully to 15 ml. chloroform in screw-capped vials (50 ml.). The vials were sealed and rotated at 6 r.p.m. in a 30 ± 0.1° water bath. Five-milliliter samples were taken at 3, 5, 7, 9, 11, 13, and 15 min. from the aqueous phase and analyzed for methysergide maleate by UV spectrophotometry.

Dissolution Rates—A 6- or 25-r.p.m. stirrer motor, fitted with a 2.54-cm. propeller blade placed 4 cm. from the bottom of an 800-ml. beaker containing 500 ml. 0.1 *N* HCl solution, was employed for these determinations. Methysergide maleate, 50 mg., or the alkaloid in combination with caffeine, prepared by mixing 50 mg.

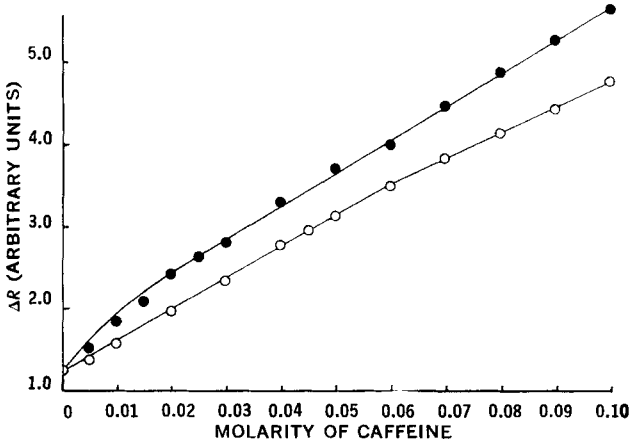

Figure 2—*Vapor pressure osmometer measurements for aqueous solutions of caffeine and combined caffeine–0.01* M *methysergide maleate. Key:* ●, *caffeine solution measurements added to measurement for a 0.01* M *methysergide maleate solution; and* ○, *measurements for combined caffeine–0.01* M *methysergide maleate solutions.*

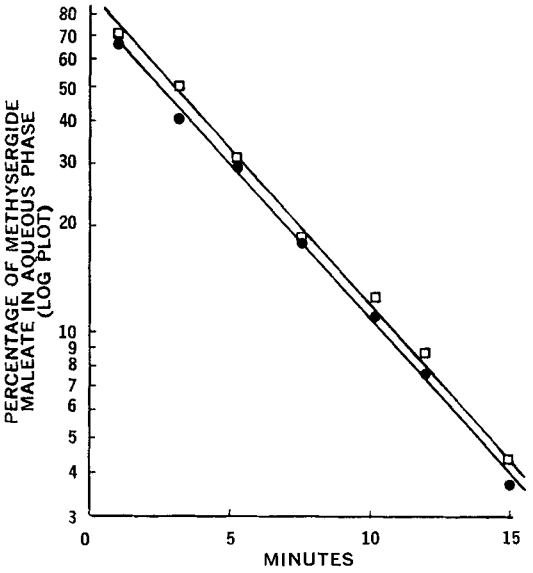

Figure 3—*Methysergide maleate–caffeine (1:100 w/w ratio). Partitioning-rate experiment in pH 6.65 0.1* M *phosphate buffer. Key:* ●, *methysergide maleate in the presence of caffeine; and* □, *methysergide maleate.*

alkaloid with 5 g. caffeine in a mortar, was placed into the stirred solution from a height of about 1.5 cm. The temperature was maintained at 37 ± 0.1° by immersing the beaker in a constant-temperature bath. Samples were withdrawn periodically for UV analysis of methysergide maleate.

RESULTS AND DISCUSSION

Methysergide maleate showed some unexpected changes in apparent solubility when combined with caffeine. The intact proteinaceous alkaloids previously studied (1–3) had all required high ratios of xanthines to effect solubilization, demonstrated a pH dependency for complexation, and gave nonlinear changes in solubility as a function of added caffeine. Methysergide maleate (Fig. 1) shows a linear dependency of apparent solubility upon the amount of caffeine added. This has been suggested to imply a 1:1 relationship between the two compounds (4, 5). These changes are apparently pH-independent because the slopes are parallel. Their displacement only reflects the variation of inherent methysergide solubility at different pH values. The difference in behavior of this ergot alkaloid derivative indicates that the cyclic polypeptide moiety present in the naturally occurring alkaloids plays an important role in their complexing behavior.

As further evidence of interaction, vapor pressure osmometry studies were performed in a manner similar to that described by Goyan and Borazan (6). These measurements differ from those of Goyan and Borazan in that the units are not expressed in ohms but rather in arbitrary units of resistance change. Since the studies were used solely to determine interaction, the units read from the instrument, which are proportional to the resistance change in ohms, were found to be sufficient.

In Fig. 2, there are two noteworthy observations. First, note the evidence of interaction from the decreased values of ΔR when solutions of caffeine in 0.01 *M* methysergide are compared to expected values. These lower values of ΔR reflect a change in the colligative properties indicative of association of molecules. Second, the breaks in the continuity of the curves appear to support the suggestion that these inflections relate in some manner to the nature of the interaction. The complexing capacity number, as indicated by Fig. 2, is approximately 3.0, which is close to the value found for sodium salicylate–caffeine interaction (6). Although the significance of complexing capacity numbers has not yet been well established, the indication here is that the methysergide maleate–caffeine and sodium salicylate–caffeine interactions are related in some manner.

After establishing an interaction, the effect of this interaction on parameters related to drug absorption was studied. The effect of the interaction on dissolution rate, which had been quite dramatic in previous studies (1–3), was negligible for methysergide maleate. Since the drug has a greater inherent solubility than the ergot alkaloids, an attempt to demonstrate dissolution enhancement by slowing the stirrer speed to 6 r.p.m. was tried but was unsuccessful. The partitioning behavior, which had paralleled *in vivo* absorption effects (2, 3), also was negligible for caffeine–methysergide maleate combinations (Fig. 3). The *in vitro* studies, therefore, suggest that the stronger interaction demonstrated in this study is possibly a deleterious factor when attempting absorption enhancement through the use of complexing agents.

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