Automated Assay of Single Tablets of Methdilazine and Methdilazine Hydrochloride

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Abstract □ An automated analytical system was used to determine the amount of methdilazine base or methdilazine hydrochloride in a single tablet. Tablets were sampled at a rate of 20/hr., with observed coefficients of variation of 2.8 and 3.4% for methdilazine base and methdilazine hydrochloride, respectively. Blending of methdilazine hydrochloride tablets was improved by presoaking the tablets in the sample cups. Interference from ascorbic acid was overcome by first blending the tablet in a basic solution containing copper (II) ion followed by acidification to solubilize the methdilazine hydrochloride prior to sampling.

Keyphrases □ Methdilazine and methdilazine hydrochloride single tablets—automated UV analysis □ UV spectrophotometry—analysis, automated, single methdilazine and methdilazine hydrochloride tablets

Methdilazine[1] (1), as the base or as the hydrochloride (I), is a potent long-acting antipruritic agent, reportedly effective in relieving a variety of itching conditions (2, 3). In this study, it was determined in two different formulations by an automated analysis system.

EXPERIMENTAL[2]

Reagents—The following were used:

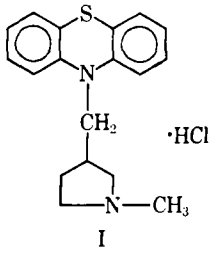
Phosphoric Acid Solution—Phosphoric acid[3], 0.1 and 2 *M* in distilled water.

Cupric Chloride Solution—Cupric chloride dihydrate[3], analytical reagent grade, 0.001% in 0.1 *M* aqueous ammonia[3], analytical reagent grade.

Alcohol Reagent—Methanol[3], analytical reagent grade, and ethanol[3], analytical reagent grade, mixed in the ratio of 3:1 v/v.

Standards—For methdilazine tablets, solutions of methdilazine base were prepared in 0.1 *M* phosphoric acid at three levels of concentration (0.333, 0.392, and 0.450 g./l.). Ten-milliliter aliquots of each solution were equivalent to 3.03, 3.56, and 4.09 mg. of methdilazine, respectively, when diluted in the Solidprep sampler.

For methdilazine hydrochloride tablets, aqueous solutions of methdilazine hydrochloride were prepared at three levels of concentration (0.748, 0.880, and 1.012 g./l.). Ten-milliliter aliquots of each solution were equivalent to 6.8, 8.0, and 9.2 mg. of methdilazine hydrochloride, respectively, when diluted in the Solidprep sampler.



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Samples—Production lots of tablets were used in this study. Theoretical tablet content was 3.6 mg. for the methdilazine tablets and 8.0 mg. for the methdilazine hydrochloride tablets.

Procedure—Schematics of the automatic analyzer systems are shown in Figs. 1 and 2.

Methdilazine tablets were disintegrated in the presence of 0.1 *M* phosphoric acid, sampled, and dialyzed. The intensity of the absorbance at 252 nm. was then measured and recorded (Fig. 3).

Methdilazine hydrochloride tablets, after pretreatment with alcohol, were disintegrated in the presence of basic cupric chloride. After 45 sec., the sample was acidified with 2 *M* phosphoric acid. This resultant solution was then sampled and dialyzed, and the drug content was measured and recorded as previously indicated. The steady-state curve of the system is shown in Fig. 4.

Tablets were sampled at a rate of 20/hr. Standard solutions were analyzed several times during the day to check for any variation in absorbance. No significant variation was observed.

Calculation—The average absorbance for each standard was plotted *versus* tablet equivalent to give a standard curve. Reference to the appropriate standard curve for each sample yielded the milligrams of methdilazine or methdilazine hydrochloride per tablet.

DISCUSSION

Methdilazine tablets contained no interfering excipient. Disinte-

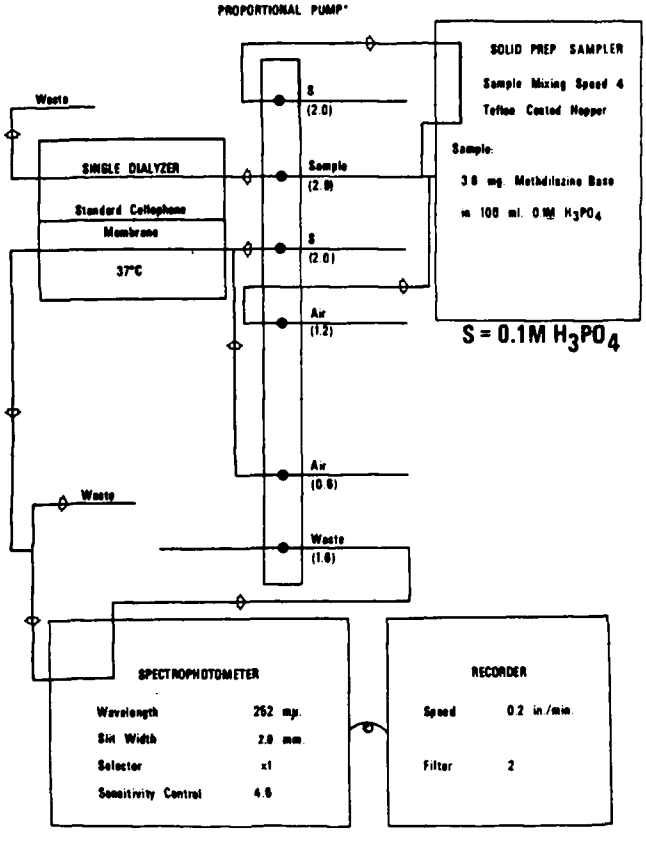

Figure 1—*Schematic for methdilazine tablets. (*Values in parentheses are flow rates in milliliters per minute. All pump tubing is Tygon.)*

[1] Tacaryl Chewable and Tacaryl Hydrochloride Tablets, Mead Johnson Laboratories, Division of Mead Johnson and Co.

[2] The analytical train consisted of the following Technicon modules (Technicon Corp., Tarrytown, N. Y.): (*a*) Solidprep sampler, (*b*) proportioning pump (model I), and (*c*) dialyzer (model I), in conjunction with a Hitachi Perkin-Elmer model 139 spectrophotometer using a microflow cell, 9120 No. 5, a Sargent model TR-05 recorder, and a Brewer model 40 automatic pipeting machine, equipped with a 50-ml. syringe (BBL, Division of BioQuest, Cockeysville, Md.).

[3] Mallinckrodt.

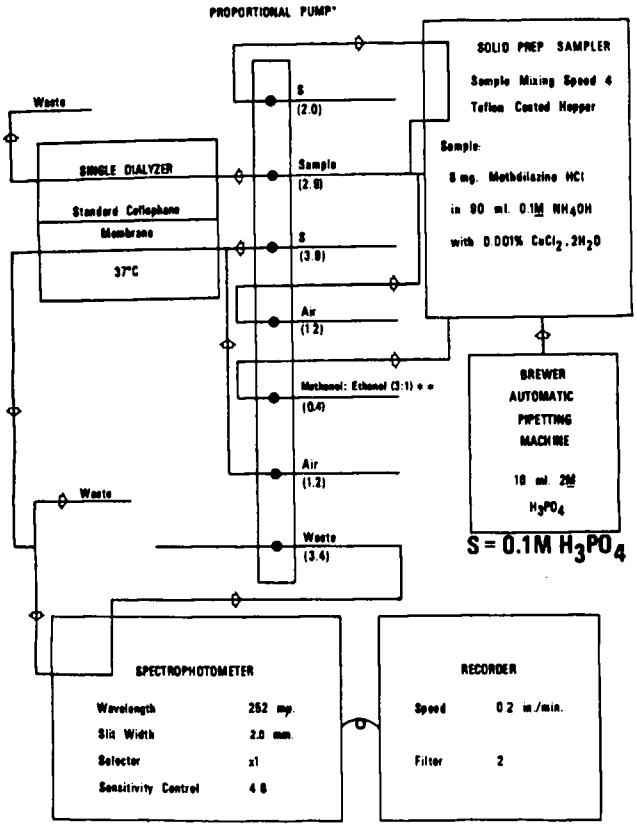

Figure 2—*Schematic diagram for methdilazine hydrochloride, 8 mg. tablets. (*Values in parentheses are flow rates in milliliters per minute. **Solvaflex tubing; all other tubing is Tygon.)*

gration in phosphoric acid followed by dialysis was sufficient to measure the drug absorbance at 252 nm.

Methdilazine hydrochloride tablets gave somewhat erratic results when assayed by the procedure developed for methdilazine tablets. Investigation indicated two factors contributing to this observation: (*a*) incomplete disintegration of the tablet in the Solidprep sampler, and (*b*) a tablet excipient that interfered in the UV measurement of drug.

Methdilazine hydrochloride tablets are manufactured as coated tablets, with a center drug-containing core. Pretreatment of individual tablets at position one on the sampler tray with 1.2 ml. of

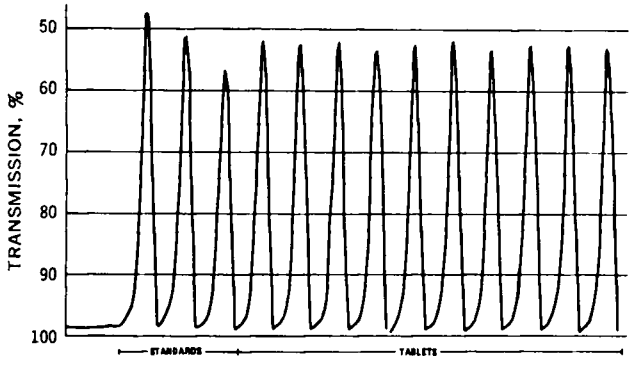

Figure 3—*Typical curve for methdilazine tablets and standards.*

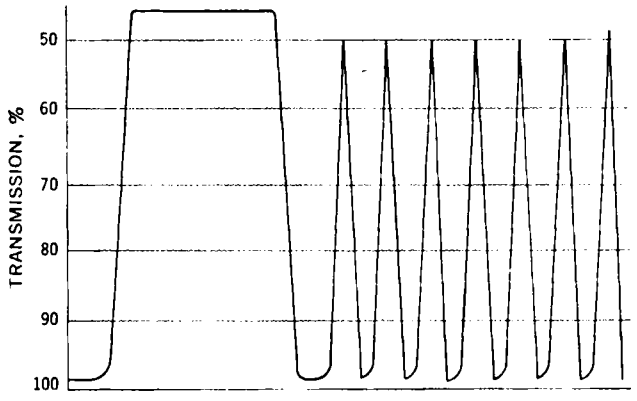

Figure 4—*Steady-state response of methdilazine hydrochloride.*

alcohol for 3 min. prior to disintegration in the sampler was sufficient to loosen the outer tablet coating.

The presence of ascorbic acid (2 mg./tablet) in methdilazine hydrochloride tablets resulted in assay values 13% above theory. This was overcome by oxidative destruction of the ascorbic acid using a cupric chloride–ammonia solution. However, methdilazine precipitated in basic solution, necessitating the addition of a sufficient amount of phosphoric acid to redissolve the methdilazine.

This requirement was met by using an automatic pipet in conjunction with the Solidprep sampler. Utilization of the cam system in the sampler allowed the addition of 2 *M* phosphoric acid 45 sec. into the analysis cycle.

Using the described analytical systems, linearity of absorbance values obtained for standards was satisfactory from 0 to 200% of declared tablet potency for both methdilazine and methdilazine hydrochloride.

RESULTS

Standard Curve—The average absorbance for each of the three standards was determined. A plot of the values gave a straight line in accordance with Beer's law.

Reproducibility of Standards—The reproducibility of the method was checked by the analysis of 30 standards (three levels of concentration) for both methdilazine and methdilazine hydrochloride. The coefficient of variation ranged from 0.3 to 0.9%.

Accuracy and Precision—The accuracy and precision of the method were ascertained by spiking a product placebo with the theoretical amount of drug prior to sampling. Data generated in this manner indicated the accuracy to be 1% with a coefficient of variation of 2.4%.

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ACKNOWLEDGMENTS AND ADDRESSES

Received December 27, 1971, from *Mead Johnson and Company, Evansville, IN 47721*

Accepted for publication February 21, 1973.

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