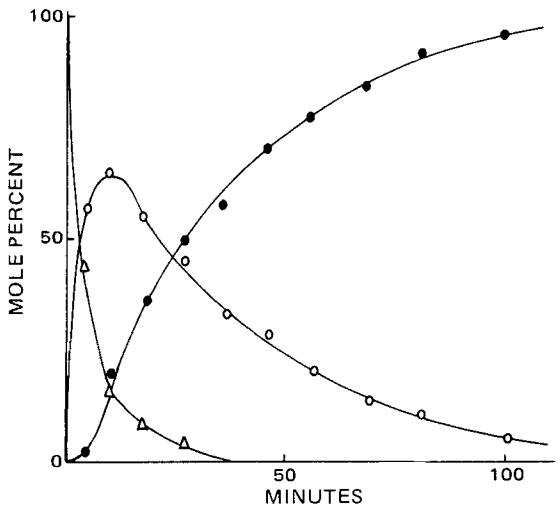

Figure 8—*Reaction profile of base-catalyzed conversion of I to III and V. A solution of I (0.863 mg/ml) in 0.05* M *sodium hydroxide at 30° under a nitrogen stream was periodically subjected to HPLC by direct injection of the alkaline mixture (pH 12.7) sample (4 μl) onto the column. Chromatographic conditions were the same as in Fig. 5. Key: △, I; ○, III; and ●, V.*

and B prostaglandins over concentration ranges of 0–30, 0–5, and 0–3 μg, respectively. In all cases, the correlation coefficient for the linear regression lines was 0.999. The minimum detection quantities of E, A, and B prostaglandins (followed at 210, 221, and 282 nm, respectively) were 150, 30, and 25 ng, respectively, when injected at a recorder range setting of 0.05 aufs.

The developed HPLC system is expected to have great utility in kinetic studies of the degradation of E and A prostaglandins. For example, Fig. 8 shows the reaction profile of base-catalyzed conversion of I to III and V. The rate constants of dehydration (0.267 min^{-1}) and isomerization (0.027 min^{-1}) were obtained by the direct analysis of the reaction species.

The described results were more rapid and sensitive than literature methods.

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Determination of Meclizine Hydrochloride by Ion-Pair Extraction with Methyl Orange

F. S. HOM ˣ and W. R. EBERT

Abstract □ A method, based on ion-pair extraction, is described for the quantification of meclizine hydrochloride in various pharmaceutical dosage forms, for content uniformity determination, and for concentration monitoring in dissolution and bioavailability studies. Methyl orange, dissolved in pH 2.8 MacIlvaine buffer, gave excellent recovery of meclizine after its isolation from aqueous solutions of gelatin, urine, and blood serum. The chloroform-extracted molecular species appeared to be a 1:1 ion-pair. Beer's law was obeyed for a wide concentration range. Because the extracted species seemed well defined and stable and since a surface or an interphase adsorption phenomenon was not a problem, the reported method is considered sensitive, accurate, precise, rapid, and simple.

Keyphrases □ Meclizine hydrochloride—spectrophotometric analysis using ion-pair extraction with methyl orange, pharmaceutical dosage forms and biological fluids □ Ion-pairs—meclizine hydrochloride–methyl orange, spectrophotometric analysis, pharmaceutical dosage forms and biological fluids □ Spectrophotometry—analysis, meclizine hydrochloride using ion-pair extraction with methyl orange, pharmaceutical dosage forms and biological fluids □ Antiemetics—meclizine hydrochloride, spectrophotometric analysis using ion-pair extraction with methyl orange, pharmaceutical dosage forms and biological fluids

Meclizine hydrochloride USP (1), an antiemetic, has been used in the management of motion sickness for many years. All available methods cited by Wong *et al.* (2), including the official ones (1), that are used for the determination of meclizine are not suitable or convenient for the rapid assay of numerous small quantities of the drug

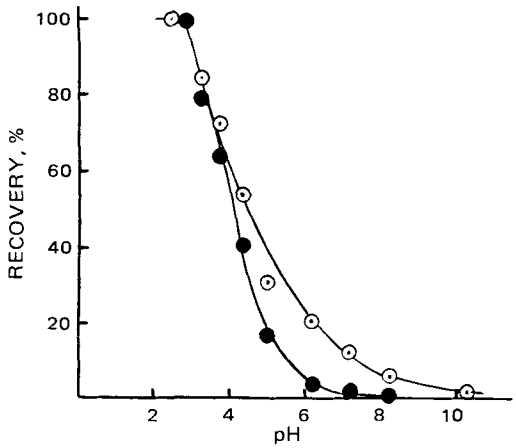

Figure 1—*Meclizine recovery pH profile after 150-ml chloroform extraction of 150-ml aqueous solution containing 2.0 × 10^{-5} M meclizine citrate, 7.6 × 10^{-5} M methyl orange, and 0.1 M dibasic sodium phosphate, which was made alkaline with sodium hydroxide and the pH was adjusted with citric acid. Key: ⊙, total meclizine extracted; and ●, meclizine extracted as methyl orange ion-pair.*

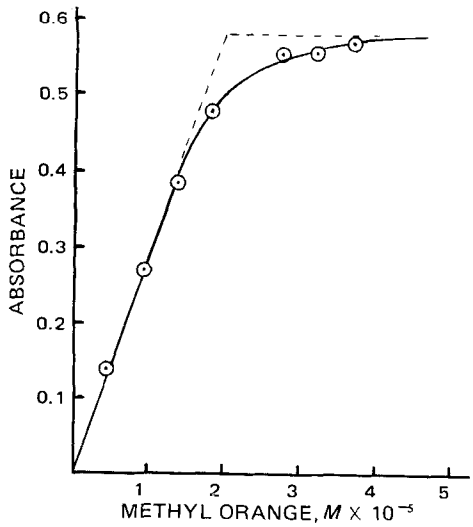

Figure 2—*Absorbance of the chloroform extract at 422 nm as a function of the methyl orange concentration with a constant 2 × 10^{-5} M meclizine in the aqueous layer.*

samples. For the Wong *et al.* (2) GLC method to be applicable to the present case, the small amounts of the isolated drug must be concentrated to a small volume, which is inconvenient.

Narrod *et al.* (3) used a modification of a literature method (4) in their study of the metabolism of meclizine in the rat. Their modified technique apparently worked well, but they experienced extraction and recovery problems. Similar analytical problems prompted the study of the chloroform extraction of meclizine from aqueous solutions (5) and the development of the present method.

EXPERIMENTAL

Apparatus—A spectrophotometer[1], matched 1-cm cells, a pH meter[2], and a rotating bottle (6) or the NF *in vitro* test apparatus (7) were used.

Reagents—USP meclizine hydrochloride reference standard, meclizine hydrochloride[3], type B gelatin[4], 25-mg meclizine hydrochloride tablets[5] and capsules[6], and analytical reagent grades of methyl orange[7], chloroform, citric acid monohydrate, dibasic sodium phosphate dodecahydrate, potassium chloride, anhydrous sodium sulfate, hydrochloric acid, and sodium hydroxide were used as received.

Methyl Orange Solution—Dissolve 250 mg of methyl orange and dilute to 1 liter with distilled water.

McIlvaine Buffer (8)—For Stock Solution A (0.2 *M*), dissolve 71.63 g of dibasic sodium phosphate dodecahydrate and dilute to 1 liter with distilled water. For Stock Solution B (0.1 *M*), dissolve 21.01 g of citric acid monohydrate and dilute to 1 liter with distilled water. To prepare pH 2.8 buffer, transfer 158 ml of Stock Solution A into a 1-liter volumetric flask and dilute to volume with Stock Solution B. Mix well and check and adjust pH, if necessary, with more Stock Solution A or B. Do not contaminate the pH 2.8 buffer solution with chloride ions from the electrode.

Reagent Solution—Dilute 100 ml of methyl orange solution to 1 liter with pH 2.8 buffer solution and mix well.

Standard Preparation—Dissolve 25 mg of USP meclizine hydrochloride reference standard, accurately weighed, by warming on a steam bath, if necessary, and dilute with 0.1 *N* HCl to volume in a 200-ml volumetric flask. Further dilute 10.0 ml with 0.1 *N* HCl to volume in a 200-ml volumetric flask.

Sample Preparation—Dissolve a sufficient sample equivalent to 25 mg of meclizine hydrochloride in 0.1 *N* HCl by warming on a steam bath, if necessary, so that the final solution contains a concentration of about 6.25 μg/ml. Adjust the pH of the solution with hydrochloric acid to a value of 1 or less.

Procedure—Concomitantly pipet 25.0-ml aliquots of standard and sample solutions into respective separators. Extract with 25 ml of chloroform by shaking for about 1 min. Allow the phases to separate and discard the aqueous layer. Wash the chloroform phase with 25 ml of 1 *N* NaOH by shaking for about 1 min and collect the chloroform layer into a 25-ml volumetric flask. Add more chloroform through the separator, if necessary, to bring to volume and mix well. Pipet 10.0-ml aliquots of the chloroform solutions into clean dry separators and use 10.0 ml of chloroform for the reagent blank. Add 20 ml of reagent solution to each. Shake each separator for about 1 min and allow the phases to separate.

Determine the absorbance of the chloroform extract at 422 nm *versus* the reagent blank in a suitable spectrophotometer after drying the extract with 1 g of anhydrous sodium sulfate. Calculate the amount of meclizine hydrochloride, in milligrams, in the sample by using:

$$\text{mg/sample} = \frac{4CA_u}{A_s} \qquad \text{(Eq. 1)}$$

where A_u and A_s are the absorbance values of the sample and standard, respectively; and C is the concentration of the standard solution in micrograms per milliliter.

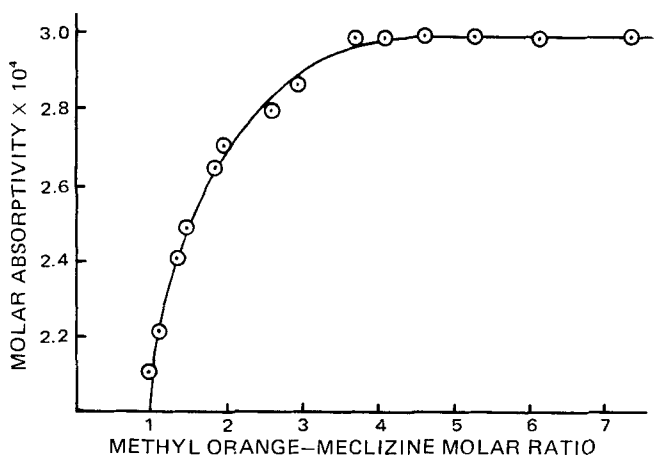

Figure 3—*Molar absorptivity of the chloroform extract at 422 nm as a function of the methyl orange to meclizine molar ratio in the aqueous layer.*

[1] Beckman model DU.
[2] Beckman Zeromatic.
[3] Napp Chemicals, Inc.
[4] Rousselot Corp.
[5] Bonine chewable tablets, 25 mg, Pfizer No. 24419.
[6] Meclizine hydrochloride gelatin capsules, 25 mg, R. P. Scherer, E-9736.
[7] Baker Chemical Co.

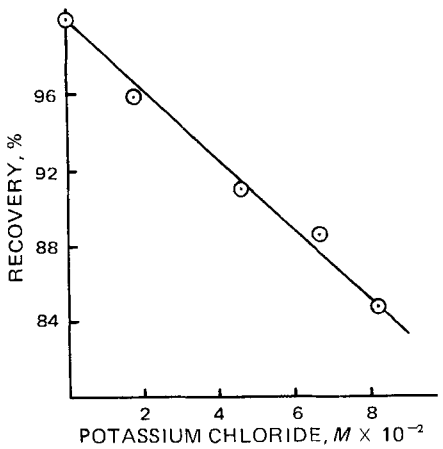

Figure 4—*Effect of chloride concentration on the percent recovery of meclizine.*

RESULTS AND DISCUSSION

It was necessary to study the effects of pH, various ions, and buffer systems to find an optimum condition for the chloroform extraction of meclizine with methyl orange (5). Figure 1 shows the percent meclizine extracted into chloroform from a citric acid–sodium phosphate–sodium hydroxide system as a function of pH (from basic to acidic). The open circles represent the total amounts of meclizine extracted into the chloroform layer, and the closed circles represent that portion extracted as the methyl orange ion-pair.

Absorbance reading at the 422-nm wavelength of the original chloroform extract from a given pH value only showed the amount of meclizine extracted as the methyl orange ion-pair (closed circles). The amount of meclizine extracted other than as the methyl orange ion-pair was visualized by a subsequent treatment of the original chloroform extract with an excess of reagent solution. The absorbance reading of the resulting chloroform layer represents the total meclizine extracted (open circles). The difference in the two curves between pH values of 4 and 10 is meclizine extracted possibly as the free base or as other ion-pairs. The shapes of the two curves indicate an apparent anomalous behavior because meclizine, an amine, should be extracted into chloroform rapidly and completely at the higher pH values but is not, probably because of the insolubility of meclizine in water (9).

This observed behavior is not reversible: if the system is made basic again, the meclizine remains in the chloroform layer. Apparently the rapid addition of alkali causes the meclizine in solution to form a colloidal suspension in water, making the complete chloroform extraction difficult and slow. Therefore, the observed difficulty may be a physical interphase phenomenon rather than a chemical one. To circumvent this difficulty, a method based on the chloroform extraction at pH 2.8, where all of the meclizine is extracted in the form of methyl orange ion-pairs, was developed.

Figure 2 is a plot of absorbance of the chloroform extract at 422 nm as a function of the methyl orange concentration with a constant 2×10^{-5} *M* meclizine in the aqueous layer. The extrapolation of the linear portions of the curve gives an intersect at about the 2×10^{-5} *M* methyl orange point, indicating an apparent 1:1 ion-pair of methyl orange to meclizine. However, a molar ratio greater than 1 must be used for the complete meclizine extraction, as indicated by the curve leveling off slowly after the intersect.

Figure 3 shows the molar absorptivity at 422 nm as a function of the methyl orange to meclizine molar ratio. As can be seen, a value of about 4 or greater is required before a constant molar absorptivity of about 2.91×10^4 is obtained. Unfortunately, Narrod *et al.* (3) did not give a value for this comparison. However, Chatten and Okamura (10) listed molar absorptivities for eight methyl orange ion-pairs ranging from 2.36 to 3.24×10^4. Their mean was 2.81 with a standard deviation of 0.33×10^4, which is close to the present value of about 2.91×10^4.

A typical Beer's law plot of absorbance at 422 nm *versus* meclizine concentration is linear if the methyl orange to meclizine molar ratio is 4 or greater and the system is freed of ions or molecules that can also form ion-pairs with meclizine or methyl orange. Figure 4 shows the effect of the chloride ion on the percent recovery of meclizine as the methyl orange ion-pair. The chloride ion competes with methyl orange to form an ion-pair with meclizine. For this reason, meclizine is converted to the free base to eliminate interfering ions before it is allowed to form the ion-pair with methyl orange.

Since this is an acid–dye method, color change could be a problem; however, the methyl orange–meclizine ion-pair in chloroform at these concentration levels was stable for 6 hr or longer, provided the chloroform was kept from evaporating. Methyl orange in the range from 2.95 to 29.5 mg/liter when dissolved in pH 2.8 McIlvaine buffer was stable for 2 weeks or longer, as shown by the constancy of the absorbance at 505 nm *versus* time in days. One fault with this reagent solution is that it supports mold growth. However, the reagent solution may be filtered and washed with chloroform before use. The absorbance of the reagent blank is zero or near zero and is unique for a colorimetric method of this type. Another property worth pointing out is surface or interphase adsorption. This phenomenon is a common source of difficulty in this type of analytical technique but is not a problem in the present method.

The extraction interphase is clean to the naked eye, perhaps the result of the use of rather dilute solutions. Glassware shows no sign of surface adsorption; consequently, special cleaning and handling are not necessary. Since methyl orange in solution exists in several forms, one has the choice of which form to use for the final absorbance reading. The cationic form has about a 30% advantage in sensitivity over the anionic form. However, use of the cationic form for the final absorbance reading requires an extra step in the procedure. For most purposes, this additional sensitivity is not necessary or worth the added effort. All recovery results reported were made on the anionic form of methyl orange.

Precision and Accuracy—Table I lists the replicate recovery results of 100 μg of meclizine hydrochloride from 20-ml solutions of water, 0.125% type B gelatin, and 50% urine. The mean recovery was from 97.0 to 100.2% of theory with a less than 1% *RSD*. Table II shows the replicate recovery results of 20 μg of meclizine hydrochloride from 20-ml solutions of water, 0.125% type B gelatin, 50% urine, and 10% blood serum. The mean recovery was from 98.5 to 99.5% of theory with a relative standard deviation of 2.5% or less. Gelatin binding of meclizine may have been the reason for the lower recovery in both cases. Table III summarizes the results on content uniformity determination of meclizine hydrochloride from 25-mg

Table I—Recovery Results of 100 μg of Meclizine Hydrochloride from 20-ml Solutions

	Wafer	0.125% Gelatin	50% Urine
	99.7	97.0	100.0
	99.7	96.0	99.4
	101.0	98.0	100.3
	99.7	97.4	99.4
	100.7	96.4	101.3
Mean ± *SD*	100.2 ± 0.6	97.0 ± 0.8	100.1 ± 0.8

Table II—Recovery Results of 20 μg of Meclizine Hydrochloride from 20-ml Solutions

	Water	0.125% Gelatin	50% Urine	10% Blood Serum
	20.0	19.5	19.7	19.2
	19.0	19.7	20.0	20.2
	20.2	20.0	19.8	20.3
	20.2	20.3	20.3	20.0
	19.8	19.2	19.4	19.7
Mean ± *SD*	19.8 ± 0.5	19.7 ± 0.5	19.8 ± 0 5	19.9 ± 0.4

Table III—Results from Content Uniformity Determinations of Meclizine Hydrochloride in Tablets and Solid Gelatin Capsules

	Milligrams per Tablet	Milligrams per Capsule
	26.0	24.4
	26.7	25.3
	25.9	25.2
	27.0	25.3
	27.3	25.5
Mean ± *SD*	26.5 ± 1.0	25.1 ± 0.4

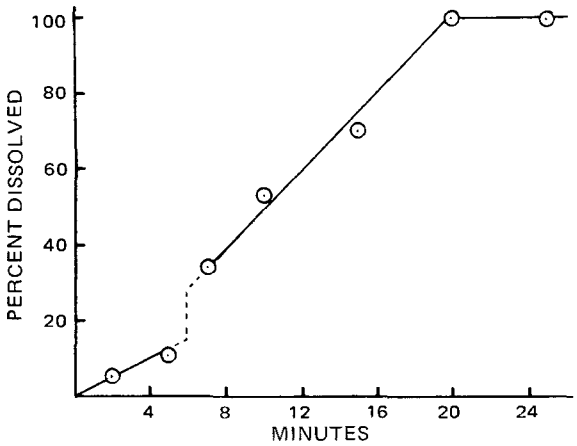

Figure 5—*Dissolution of meclizine hydrochloride from a 25-mg solid gelatin capsule in simulated gastric fluid (without pepsin) at 37° using the rotating-bottle method.*

solid gelatin capsules and 25-mg tablets. The mean recovery was 100.4 and 106.0% of labeled claim with relative standard deviations of 1.6 and 4.0%, respectively.

Figure 5 shows the dissolution of meclizine hydrochloride from a 25-mg solid gelatin capsule in simulated gastric fluid (without pepsin) at 37° using the rotating-bottle method (6,7). The initial portion of the curve represents the dissolution of the drug from the shell. When the shell dissolved, the slope of the curve changed from the dissolution of meclizine hydrochloride in the lesser concentrated shell to the more concentrated core. The core completely dissolved after about 20 min and the curve leveled off.

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Recording pH Method of Characterizing Composition and Monitoring Dissolution Profile of an Anhydride–Acid Copolymer and Its Salt Derivatives

YEHCHUN MO, GARNET E. PECK, ALLEN HEYD, and GILBERT S. BANKER [x]

Abstract □ A sensitive potentiometric monitoring method was developed that permits the continuous measurement of the dissolution profiles of methyl vinyl ether–maleic anhydride–acid copolymers and salt derivatives. Three distinct rate periods were observed in the dissolution of the anhydride copolymer. The relative dissolution rate of the anhydride copolymer, expressed as percent anhydride dissolved, was independent of sample weight over the weight range studied. The acid form of the copolymer showed only one dissolution rate period, with dissolution being very rapid. The rapid initial pH decrease observed during the first stage of dissolution for a series of anhydride–acid copolymer powder samples correlated closely with the anhydride–acid ratio, permitting chemical characterization of the copolymer functionality simultaneously with the analysis of dissolution profiles. Similarly, the extent of copolymer alkaline salt conversion was inversely proportional to the initial maximum pH increase observed during the first stage of dissolution of these salts. Mechanisms of dissolution of copolymer powder materials are discussed and compared to the dissolution of compressed disks and films reported previously.

Keyphrases □ Maleic anhydride–acid copolymers—with methyl vinyl ether, potentiometric characterization of composition and measurement of dissolution profiles □ Methyl vinyl ether–maleic anhydride–acid copolymers—potentiometric characterization of composition and measurement of dissolution profiles □ Copolymers—methyl vinyl ether–maleic anhydride–acid, potentiometric characterization of composition and measurement of dissolution profiles □ Potentiometry—characterization of composition and measurement of dissolution profiles of methyl vinyl ether–maleic anhydride–acid copolymers □ Dissolution—methyl vinyl ether–maleic anhydride–acid copolymers, potentiometric measurement of profiles

Alkyl, aryl, and alkyl vinyl ether–maleic anhydride copolymers, their hydrolyzed acids, and various ester derivatives have been recommended for various pharmaceutical applications, including use as thickeners, suspension and emulsion stabilizers, topical product and cosmetic vehicles, complexing agents of iodine and other antiseptics, controlled-release matrixes, and protective, delayed-, or controlled-release coatings (1–4). Styrene,