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Analysis of Homatropine Methylbromide Dosage Forms

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Abstract ☐ A stability-indicating method of analysis for homatropine methylbromide in pharmaceutical formulations was developed. This method is based on the formation of a picric acid–quaternary ammonium complex, which is adsorbed on acid-washed diatomaceous earth in alkaline media followed by on-column chloroform extraction. The picrate complex is measured spectrophotometrically at 365 nm. The method was selective for homatropine methylbromide in that there was no interference from its major hydrolytic decomposition products, tropinium methylbromide and mandelic acid.

Keyphrases ☐ Homatropine methylbromide—spectrophotometric analysis, pharmaceutical formulations ☐ Spectrophotometry—analysis, homatropine methylbromide in pharmaceutical formulations ☐ Anticholinergic agents—homatropine methylbromide, spectrophotometric analysis in pharmaceutical formulations

Previously reported assay methods employed in the analysis of homatropine methylbromide dosage forms involved the precipitation of an insoluble salt of the methylhomatropine cation by anions such as the reineckate, silicotungstate, and tetraiodomercurate, followed by colorimetry (1) or turbidimetry (2, 3). Other colorimetric procedures involved chromogenesis with Dragendorff's reagent (4, 5) or measurement of the ferric hydroxamate complex (6). Analytical methods utilizing spectrophotometry (7, 8), TLC (9), and GLC (10, 11) also were reported. As previously discussed (12), these methods and official procedures (13) lack sensitivity, selectivity, or specificity or require additional washing or separation steps.

The stability-indicating assay procedure for homatropine methylbromide in syrups (12) is time consuming. This report presents a simple stability-indicating method, a modification of the method of Chin and Lach (14), for the assay of homatropine methylbromide dosage forms. The procedure was applied, with satisfactory results, to several commercial tablets, drops, and elixirs.

EXPERIMENTAL

Instruments—The recording spectrophotometer[1] had 1-cm cells and glass tubing columns[2], 200 × 25-mm o.d. with a tip 50 × 8-mm o.d. The columns were fitted with a small wad of glass wool at the bottom and top of the packing.

Materials and Reagents—The following were used: acid-washed diatomaceous earth[3]; homatropine methylbromide (NF reference standard); ammonium picrate reagent prepared by dissolving 11.2 g of picric acid[4] in 900 ml of distilled water, adding 6 ml of concentrated ammonia[4], and diluting to 1000.0 ml with distilled water; mandelic acid[4]; tropinium methylbromide[5]; and chloroform[4].

Standard Curve—A stock solution of homatropine methylbromide was prepared by dissolving 50.0 mg in 100 ml of distilled water. Further dilutions were made to obtain homatropine methylbromide standard solutions containing 0.125, 0.25, and 0.375 mg/ml. Two milliliters of stock and diluted standard solutions were each transferred into a 100-ml beaker containing 3.0 g of acid-washed diatomaceous earth, and 1.0 ml of ammonium picrate reagent was added. The mixture was mixed thoroughly and quantitatively transferred and packed into the glass column.

Elution was accomplished by immediately passing 17 × 5-ml portions of water-saturated chloroform at a flow rate of 7–9 ml/min, allowing each portion of eluant to run completely into the column before adding the next. The combined eluates were collected separately in 100-ml volumetric flasks and diluted to volume with chloroform. The absorbance of the standard solutions was measured in 1-cm absorption cells at 365 nm against chloroform as a blank.

Sample Procedure—*Tablets*—A number of tablets, equivalent to about 50 mg of homatropine methylbromide, were transferred to a 100-ml volumetric flask, and 75 ml of distilled water was added. The flask was shaken well for 30 min, and distilled water was added to the mark. The mixture was filtered through fluted filter paper, and the first 10 ml of filtrate was rejected. Two milliliters of the filtrate was pipetted into a 100-ml beaker, and the test was conducted as described under *Standard Curve*, beginning with "containing 3.0 g of acid-washed diatomaceous earth, ... "

Drops or Elixir—A volume of drops or elixir, equivalent to about 50 mg of homatropine methylbromide, was accurately measured and transferred to a 100-ml volumetric flask. Distilled water was added to the mark, and the contents were mixed well. Two milliliters was pipetted into a 100-ml beaker, and the test was conducted as described under *Standard Curve*, beginning with "containing 3.0 g of acid-washed diatomaceous earth, ... "

RESULTS AND DISCUSSION

This method, a modification of the one of Chin and Lach (14), is based on the reaction of picric acid with quaternary ammonium compounds in an alkaline medium to form a colored complex. The complex is adsorbed on acid-washed diatomaceous earth and measured spectrophotometrically after on-column extraction with water-saturated chloroform.

Under the experimental conditions, a linear relationship existed between the absorbance and concentration of homatropine methylbromide over the 0.25–1.0-mg/ml concentration range, with a correlation coefficient of 0.9996. Regression analysis showed that the regression equation was $y = 0.421x - 0.003$, with a standard error of the estimate of y on x

[1] Coleman-Hitachi model EPS-3T.
[2] SGA Scientific Inc., Bloomfield, N.J.
[3] Celite 545, Johns-Manville, Denver, Colo.
[4] Analytical grade, J. T. Baker.
[5] Endo Laboratories, Inc., Garden City, N.Y.

Table I—Reproducibility of Colored Complex of Replicate Homatropine Methylbromide Samples Containing 0.5 mg/ml

Solution	Absorbance
1	0.421
2	0.427
3	0.424
4	0.423
5	0.422
6	0.426
7	0.425
8	0.421
9	0.422
Average	0.423
CV	0.52%

of 0.005 and standard errors of the estimate of the intercept and slope of 0.05 and 0.84, respectively. The colored complex in chloroform was stable for at least 5 hr.

The precision of the assay procedure was determined by running replicate studies on nine 2.0-ml aliquots of a standard homatropine methylbromide solution containing 0.5 mg/ml. Each solution was assayed by the proposed procedure. The coefficient of variation for the nine replicate samples was 0.52% (Table I). A blank sample, containing tropinium methylbromide and mandelic acid equivalent to 100% hydrolytic degradation of homatropine methylbromide, assayed by the proposed procedure yielded no absorbance at 365 nm, demonstrating that the method is stability indicating.

Table II—Results of Analysis of Commercially Available Homatropine Methylbromide Dosage Forms

Dosage Form	Amount Claimed, mg/Tablet or mg/ml	Percent of Claim Found[a]			
		Proposed Method	±*SD*	Ion-Exchange Method	±*SD*
Tablet[b]	5	98.4	0.47	98.5	0.14
Elixir[c]	1	99.6	0.36	98.8	0.30
Tablet[d]	5	97.8	0.58	97.5	0.88
Elixir[e]	1	101.0	0.71	101.2	1.90
Tablet[f]	5	95.1	0.11	95.1	0.23
Tablet[g]	2.5	91.3	0.83	91.9	0.46
Drops[h]	0.27	104.0	0.57	102.6	0.40
Tablet[i]	2.5	104.0	0.75	103.5	0.11

[a] Average of three assays. [b] Mesopin tablets, Endo Laboratories Pharm. [c] Mesopin elixir, Endo Laboratories Pharm. [d] Mesopin PB tablets, Endo Laboratories Pharm. [e] Mesopin PB elixir, Endo Laboratories Pharm. [f] Cholan V tablets, Pennwalt. [g] Cholan HMB tablets, Pennwalt. [h] Sedadrops, Merrell-National. [i] Gustase Plus tablets, Geriatric Pharmaceutical Corp.

Results obtained by applying the procedure to commercially available homatropine methylbromide dosage forms are presented in Table II. Comparison of the experimental data with those obtained using an ion-exchange method (12) shows a good correlation.

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Physical Form as a Determinant of Effect of Buffered Acetylsalicylate Formulations on GI Microbleeding

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Abstract ☐ During a 48-day period, 12 male dogs received four buffered sodium acetylsalicylate formulations, quantitatively virtually identical (a homogeneous disintegrating swallow tablet, a swallow tablet in which the sodium acetylsalicylate was contained in a dissolving core, an encapsulated powder, and an aqueous suspension), at 650-mg aspirin equivalent doses twice daily during four 7-day treatment periods (each preceded by a 5-day period of no treatment) in a complete changeover fashion. Mean daily fecal blood losses of 0.75, 1.37, 1.43, and 2.89 ml were observed in the 12 dogs during treatment with the aqueous suspension, the homogeneous tablet, the encapsulated powder, and the core tablet, respectively. These findings indicate that the physical form of buffered acetylsalicylate formulations is a critical factor in the effect of such formulations on GI microbleeding.

Keyphrases ☐ Sodium acetylsalicylate—buffered formulations, various dosage forms, effect on GI microbleeding, dogs ☐ Aspirin, sodium salt—buffered formulations, various dosage forms, effect on GI microbleeding, dogs ☐ GI microbleeding—buffered sodium acetylsalicylate, effect of various dosage forms, dogs ☐ Dosage forms—buffered sodium acetylsalicylate, effect on GI microbleeding, dogs ☐ Analgesics—sodium acetylsalicylate buffered formulations, various dosage forms, effect on GI microbleeding, dogs

Gastric mucosal irritation, reflected in increased fecal occult blood loss, is a common side effect of orally administered aspirin. Levy (1) suggested that the degree of gastric mucosal erosion following the oral administration of aspirin is related to two factors: the concentration of aspirin in solution and the duration of contact of the so-