Assay of Mephentermine and Its Preparations

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Abstract □ Mephentermine sulfate is assayed by direct titration in glacial acetic acid with perchloric acid titrant and *p*-naphtholbenzein indicator. Mephentermine sulfate tablets are assayed by mixing the finely powdered sample with purified siliceous earth and magnesium oxide held in a fritted-glass filtering funnel, moistening the mixture with water to release the base, eluting the base with warm chloroform, receiving the eluate in glacial acetic acid, and titrating it with perchloric acid using *p*-naphtholbenzein indicator. Individual tablets are assayed by receiving the eluate into 10.0 ml. of 0.1 *N* sulfuric acid, shaking to extract the base from the chloroform, and determining the mephentermine spectrophotometrically using the base-line correction method proposed by Rotondaro and the assayed tablet mixture as the standard. Mephentermine sulfate injection is assayed by adsorbing the sample into a controlled amount of siliceous earth-magnesium oxide mixture and proceeding with elution and titration as for the tablets. Loss in drying specifications for mephentermine sulfate are supported by thermogravimetric data.

Keyphrases □ Mephentermine sulfate and dosage forms—analysis □ Identity tests—mephentermine □ Colorimetric analysis—titration □ Perchloric acid—titrant □ *p*-Naphtholbenzein—indicator

The synthesis of mephentermine was first reported in a patent issued to Wm. F. Bruce *et al.* in 1952 (1). A second method of synthesis was patented in 1954 (2). The material is currently available as the sulfate salt for use intravenously and intramuscularly as a sympathomimetic vasopressor.

Data for analysis of mephentermine base used in an inhaler appeared in *Drug Standards* in 1957 (3). General methods for phenylethylamine drugs were developed by Rotondaro in 1957 (4–6) involving dissolution of the sample in sulfuric acid, extracting the base with chloroform from an alkaline solution, re-extracting the base into sulfuric acid, and determining its concentration by UV spectrophotometry using a baseline correction method. A method for the assay of mephentermine in pharmaceutical preparations by colorimetric determination of the chloroform-extracted ion-pair formed with bromcresol green was reported by Horioka in 1957 (7).

Mephentermine sulfate and mephentermine sulfate injection were recognized by the *British Pharmacopoeia*, 1963 (8) and the *National Formulary* XII (9) and have been admitted to *the United States Pharmacopeia* XVIII.

EXPERIMENTAL

Identifications—Mephentermine is identified by standard tests for nitrogenous bases such as precipitation with triiodide, iodomercurate, and trinitrophenolate ions.

The melting point (154–158°) of the isolated trinitrophenolate (picrate) is another distinguishing characteristic.

The sulfate portion is identified by the usual precipitation of barium sulfate.

Loss on Drying—The NF XII monograph requires drying at 105° for 3 hr. This specification appears to be correct. Partially dehydrated mephentermine sulfate slowly takes up moisture. A single sample examined over a course of 4 months showed a variable moisture content of from a little more than 4 to 7.81%. The theoretical moisture content of the dihydrate is 7.82%.

Loss in weight of a portion of the sample was 7.65% by drying at 105° for 3 hr. There was no change in weight on drying at 120° for an additional 2.5 hr. Examination of another portion of this material on the thermobalance showed a weight loss of 7.64% in good agreement with oven drying. Rerunning the same material after exposure to atmospheric moisture gave a value of 7.81% in good agreement with the theoretical moisture content for the dihydrate.

The ready loss of moisture can be seen from the thermobalance plot of weight *versus* temperature (Fig. 1). The loss of moisture commences about 40° and is completed at 80°. There is no further loss in weight up to 122° at which temperature a very slow loss commences. This is thought to be due to loss of mephentermine with formation of the 1:1 sulfate salt. Decomposition starts about 135° with charring and there is steady loss in weight at higher temperatures.

Assay for Mephentermine Sulfate—Because of the uncertainty in moisture content, all assays were performed on material dried at 105° to constant weight (3 hr.).

Systems examined were acetic anhydride using malachite green indicator, acetic acid with crystal violet indicator, acetic acid with quinaldine red indicator, and acetic acid with *p*-naphtholbenzein indicator. Only the last system gave a sharp endpoint and was considered for further study. Potentiometric titration simultaneous with indicator endpoint showed that the endpoints by both methods were identical. The following method was adopted.

Weigh accurately about 300 mg. (250 mg. of dried sample) of mephentermine sulfate and dissolve it in 50 ml. of glacial acetic acid. Add 4 drops of *p*-naphtholbenzein indicator and titrate with 0.1 *N* perchloric acid to a green endpoint. Perform a blank determination and make any necessary correction. Each milliliter of 0.1 *N* perchloric acid is equivalent to 42.46 mg. of $(C_{11}H_{17}N)_2 \cdot H_2SO_4$.

Assay in triplicate gave a recovery of 99.8 ± 0.3% with a range of 99.5 to 100.0%.

The indicator solution is prepared by dissolving 0.4 g. of *p*-naphtholbenzein in 100 ml. of glacial acetic acid. The solution should not be stored more than 1 month.

Assay of Mephentermine Sulfate Injection—A new method for the extraction of amines from solutions of their salts has been developed. It is intended to apply this general method to other systems. The key to the method is a preparation of alkaline diatomaceous earth made by mixing magnesium oxide (chromatographic grade) with ten times its weight of diatomaceous earth.[1] To a coarse-frit sintered-glass funnel arranged for suction filtration is added 1 g. of the mixture plus 1 g. for each milliliter of solution sample. The sample is added and incorporated in the mixture. The free base liberated is eluted with five small portions of chloroform. The eluates are received in glacial acetic acid and titrated with standard perchloric acid in glacial acetic acid. The specific application to mephentermine sulfate injection follows.

Transfer to a coarse-frit sintered-glass funnel 5 g. of alkaline diatomaceous earth. Add an accurately measured volume of Mephentermine sulfate injection equivalent to about 60 mg. of Mephentermine and mix well. Extract with 15, 10, 10, 10, and 10 ml. of chloroform, mixing each portion thoroughly with the contents of the crucible then draining with the aid of gentle suction. Collect the eluates in 40 ml. of glacial acetic acid, add 6 drops of *p*-naphtholbenzein indicator, and titrate with 0.1 *N* perchloric acid to a green endpoint. Perform a blank titration and make any necessary correction. Each milliliter of 0.1 *N* perchloric acid is equivalent to 16.33 mg. of $C_{11}H_{17}N$ (mephentermine).

Potentiometric titration of the eluates simultaneous with indicator

[1] Celite 545, Johns-Manville Products Corp., New York, N. Y.

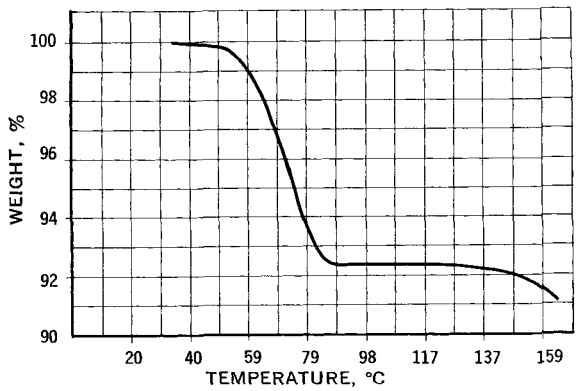

Figure 1—*Thermobalance plot of weight* versus *temperature for mephentermine sulfate.*

determination of the endpoint showed that both methods gave the same results.

Two recovery series were run, one prepared by dissolving 0.8942 g. of dried mephentermine sulfate in 40.0 ml. of water, the other by dissolving 0.5004 g. of dried mephentermine sulfate in enough water to make 25.00 ml. Seven replicate assays of 4-ml. aliquots of the first solution gave an average recovery of 99.2 ± 1.0% with a range of 98.4 to 101.0%.

Three replicates of 4-ml. aliquots of the second solution gave an average recovery of 100.3 ± 0.4% with a range of 100.0 to 100.7%.

DISCUSSION

The directions call for an indicator blank. If titration is carried out to the first color change, the blank is less than 1 drop (0.01 ml.); however, it is believed that some analysts will use the characteristic vivid green color. Titration to this point will give blanks of 0.02 to 0.05 ml.

The methods proposed are very much more rapid than those official in NF XII. The extraction process suggested for mephentermine sulfate injection is completed in less than 10 min. The results obtained, even though limited in number, appear to be within the expected analytical error.

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Fluorometric Determination of Atropine and Hyoscyamine in Tablets and Injections

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Abstract □ A fluorometric method has been developed for the quantitative determination of atropine and hyoscyamine in the presence of other belladonna constituents. Atropine and/or hyoscyamine is extracted with chloroform from basic solution, and an aliquot of the extract is added to a chloroform solution of eosine yellowish. This solution, appropriately diluted, is read on a fluorometer at an excitation wavelength of 475 mμ and an emission wavelength of 552 mμ. Scopolamine, atroscine, and other components do not produce a measurable fluorescence in this procedure and thus need not be separated from atropine or hyoscyamine.

Keyphrases □ Belladonna alkaloid dosage forms—analysis □ Atropine, hyoscyamine—determination □ Eosine yellowish—reagent □ Fluorometry—analysis

l-Hyoscyamine and atropine (*dl*-hyoscyamine) have become prominent anticholinergic and mydriatic agents (1). They are incorporated, alone or with other drugs (*e.g.*, scopolamine, barbiturates, and vitamins), in tablets, elixirs, injections, and capsules. Present official methods for the determination of atropine include a base-chloroform extraction followed by an acid-base titration (2), a base-chloroform extraction followed by a quantitative IR determinative step (3), and a perchloric acid titration in acetic acid (4). These procedures require relatively large amounts of atropine. Atropine, however, usually appears in submilligram amounts in most dosage forms.

A review of the literature revealed that much work has been done on the quantitative determination of tropane alkaloids in plant material and in commercial drug products. Most analytical approaches were characterized by colorimetric and titrimetric determinative steps. Nin'o (5) determined atropine in aluminum hydroxide with belladonna tablets using a column separation followed by reaction with *p*-dimethylaminobenzaldehyde. Zielinska-Sowicka *et al.* (6), Niezgodzki