Table II—Comparison of Assay Methods for Mestranol in Commercial Samples

Sample	Progestin Present	Mestranol Declared, mg.	% of Amount Declared by— UV	Color	Fluorometric
1	Norethynodrel	0.1	85.1[a]	99.0[a]	100
2	Ethynodiol diacetate	0.1	98.0	—[b]	104
3	Norethindrone	0.1	100	99.0	101
4	Norethindrone	0.1	95.4	100	99.7
5A[c]	—	0.08	102	102	102
5B[c]	Chlormadinone acetate	0.08	101[a]	—[b]	—[b]

[a] Corrected for interference in the spectrum. [b] Interferences prevented accurate calculations. [c] Sequential-type tablets.

The method is also applicable to single-tablet analyses. Assay values for 10 tablets ranged from 98.5 to 105% of declared values.

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Assay of Emetine Hydrochloride Injection

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Abstract □ Data are presented for the DAB 7 assay of emetine hydrochloride and for quantitative assay of emetine hydrochloride injection by a method previously reported for injections of amin-salts. The method involves nonaqueous titration of a chloroform. eluted sample from a magnesium oxide–siliceous earth mixture Thermogravimetric data show that emetine hydrochloride forms no stable hydrates, that water can be lost even at room temperature, and that loss still continues slowly beyond the usual drying temperature so that it is difficult to render the material anhydrous. For these reasons, it is suggested that emetine hydrochloride and emetine hydrochloride injection be labeled with the content of anhydrous emetine hydrochloride. Permissible variation should be ±1% for emetine hydrochloride and ±5% for the injection.

Keyphrases □ Emetine HCl injection—analysis □ Potentiometric titration—analysis □ Titrimetry—analysis

Emetine Hydrochloride Injection USP XVII has a peculiar definition in that "it contains an amount of anhydrous emetine hydrochloride ($C_{29}H_{40}N_2O_4 \cdot 2HCl$) equivalent to not less than 84% and not more than 94% of the labeled amount of emetine hydrochloride" (1). Thus it is the only pharmaceutical preparation formulated at less than 100% of label claim. This peculiar definition is necessitated by the official definition of Emetine Hydrochloride USP XVII as a hydrate of uncertain composition, which "contains not less than 98.0% and not more than 101.5% of $C_{29}H_{40}N_2O_4 \cdot 2HCl$, calculated on the anhydrous basis" (2).

Water is determined as follows: "Dry it at 105° for 2 hr.: it loses not less than 8% and not more than 14% of its weight" (2). The average water content of the solid is thus 11%, which corresponds to the average requirement for the injection of 89% of anhydrous material.

An attempt was made to assay emetine hydrochloride injection by a previously proposed method (3). The method involves distributing the sample over a mixture of magnesium oxide and purified diatomaceous earth held on a sintered-glass filtering funnel, eluting the

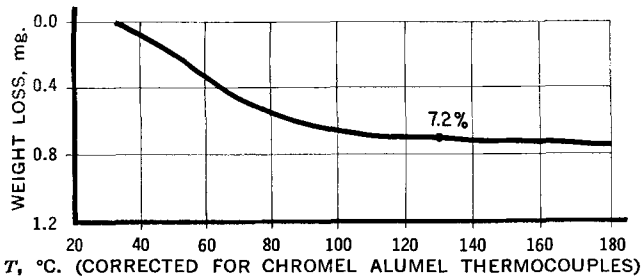

Figure 1—*Thermogravimetric study of emetine hydrochloride.*

liberated base with chloroform, and titrating the eluates with perchloric acid. However, due to the low requirement in meeting label claims, this could not be used as a guide to recovery. Therefore, a more extensive investigation was pursued.

EXPERIMENTAL

Procedure A—Weigh accurately 170 mg. of emetine hydrochloride, previously dried at 105° for 3 hr. Dissolve it in 40 ml. of glacial acetic acid; add 10 ml. of mercuric acetate T.S. and 6 drops of 0.25% *p*-naphtholbenzein in glacial acetic acid. Titrate to the green end-point. Perform a blank titration and make any necessary correction. Concomitantly determine the end-point potentiometrically. This is essentially the method of DAB 7 (4).

Weigh an amount of dried, assayed emetine hydrochloride, equivalent to 325.0 mg. of anhydrous salt, and dissolve in enough distilled water to make 5.00 ml. Assay by *Procedure B*.

Procedure B—Distribute 2.00 ml. of the solution over 3 g. of a mixture of 1 g. of chromatographic magnesium oxide and 10 g. of high flowrate, purified siliceous earth[1] held on a coarse-porosity, sintered-glass filtering funnel. Elute with five 10-ml. portions of warm (55°) chloroform, mixing each portion well with the contents of the crucible and then draining with gentle suction into 40 ml. of glacial acetic acid. Add 6 drops of *p*-naphtholbenzein indicator and titrate to the green end-point. Perform a blank titration and make any necessary correction. Concomitantly, determine the end-point potentiometrically (3).

The content of anhydrous emetine hydrochloride in the dried material found by duplicate titration by *Procedure A* was: potentiometric, 97.535 ± 0.077%; and indicator, 98.250 ± 0.084%.

Recovery from the standard solution found by duplicate titration by *Procedure B* was: potentiometric, 98.92 ± 0.25%; and indicator, 99.03 ± 0.15%.

Recovery from a commercial injection found by triplicate determination was 87.66 ± 0.76%, using the indicator end-point.

DISCUSSION

Data for recovery of assayed material show that the proposed method for the injection is accurate and reproducible enough for use as a method of control. Recovery from the commercial product is satisfactory in view of an 89 ± 5% requirement. The authors were troubled, however, by the low result obtained in the assay of the supposedly anhydrous solid, which differs significantly from 100% and barely meets the 98.0% minimum required if the indicator end-point value is taken. The sample used had been dried to constant weight, as shown by drying for an additional hour, so that the discrepancy was difficult to explain.

A sample of the original material was submitted for thermogravimetric analysis. A copy of the record is shown in Fig. 1 for a 10.8-mg. sample heated at 5°/min. in a nitrogen atmosphere. From this it can be concluded that:

1. Emetine hydrochloride forms no stable hydrates.
2. Water loss takes place even at room temperature. This usually indicates that the water content of the solid will fluctuate with the relative humidity.
3. Slow loss continues to take place at temperatures above 105°, so that the drying time specified in USP XVII would not be expected to remove all moisture. Moisture loss is so slow, however, that the sample will appear to have reached constant weight by the usual criterion. It is suggested, therefore, that emetine hydrochloride be defined in terms of its content of anhydrous salt without drying. The definition should then read: "contains not less than 99% and not more than 101% of the labeled content of anhydrous emetine hydrochloride." The injection should also be labeled in terms of content of anhydrous salt.
4. A new sample of emetine hydrochloride was obtained for moisture determination by the Karl Fischer titrimetric method (5). The reagent was standardized in triplicate against sodium tartrate dihydrate containing 15.61% water to yield a value of 6.276 ± 0.021 mg. H_2O/ml. The moisture in the emetine hydrochloride sample, determined in duplicate, was 9.40 ± 0.01%. Moisture content by drying to constant weight was 9.27%. This finding again shows that drying to constant weight does not quite remove all of the moisture. The close agreement between the oven-drying method and the Karl Fischer method suggests that the titrimetric procedure should be adopted.

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