Worrall, D. E.
Some hydroxy and amino esters of yohimbic acid
J. Am. Chem. Soc., 55 (1933), 3715

CLINICAL METHODS.

Gfeller, Hans
Contrast materials for clinical tests
Pharm. Acta Helv., 8 (1933), 131

Monnet, R.
Detection of quinine in urine by the erythroquinine reaction
J. pharm. chim., 18 (1933), 94

AN ASSAY METHOD FOR FLUIDEXTRACT OF IPECAC, U. S. P.*

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INTRODUCTION.

Several different methods for the assay of Fluidextract of Ipecac have been proposed since the method of the U. S. P. X has been found to yield troublesome emulsions. The methods of Palkin and Watkins (1), the automatic extractor method of Palkin, Murray and Watkins (2) and a modified U. S. P. IX method were reported by Bliss and collaborators (3). Other methods considered were those of Leger (4) and the British Pharmacopœia method (5).

After careful study of these methods two were thought to be worthy of further work by collaborators and a third method which is essentially the U. S. P. Type C Assay Method with certain modifications were proposed. These three methods were compared with the present U. S. P. X method.

METHODS.

1. U. S. P. X Method.—Follow U. S. P. Type Process D, using plenty of ether in the first shake-outs, continue extractions until no cloudiness results when tested with mercuric potassium iodide, if possible. Do not allow final ether solution to go to dryness on the steam-bath, but add 2 or 3 cc. of alcohol or ether to the last few cc. remaining; again evaporate to 2 or 3 cc. and add 0.1*N* H_2SO_4 before evaporating off last traces of solvent.

2. Palkin and Watkins Method (Hand Extraction).—Measure 20-cc. sample into a 100-cc. volumetric flask, add about 5 cc. *N* sulphuric acid and evaporate on a steam-bath with the aid of a current of air to about 10 cc. Then, while rotating the flask, add about 30 cc. of water; cool and make up to the mark with water. Mix well and allow to stand over night. Decant the supernatant liquid through a dry filter, rejecting the first few cc. Then proceed by either Method 2 or 3. Pipette 20-cc. filtrate (representing 4-cc. original sample) into a separatory funnel. Add 2 cc. of ammonia T.S. and completely extract the alkaloids with peroxide-free ether until no cloudiness results with potassium mercuric iodide. Evaporate the combined ether solutions on steam-bath and finish as directed in U. S. P. X, using precautions under No. 1 about evaporating last traces of solvent.

3. Palkin, Murray and Watkins (Automatic Extractor).—Pipette 20 cc. of filtrate (in Method 2) into an automatic extractor for liquids lighter than water which has been fitted to a 200-cc. flask. Add 50 cc. of water, 2 cc. of ammonia T.S. and 50.0 cc. of peroxide-free ether, shake gently to prevent deposition of solid matter on bottom of extractor; then add ether until about 75 cc. have passed into the flask. Extract on a steam-bath for about two hours. Separate

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ether from the aqueous layer and add to main concentrate in the flask. Evaporate and titrate as directed in U. S. P. X, using precautions under No. 1 about evaporating last traces of solvent.

4. U. S. P. Type C Process.—Proceed as U. S. P. X Type Process C for fluidextracts, using 10-cc. sample and 100 cc. of ether. Shake and allow to stand over night and shake again, as directed in U. S. P. Decant a 50-cc. aliquot representing 5 cc. of sample. Carry out evaporation and titration as under No. 1.

The fluidextract used was carefully prepared from ipecac furnished by the U. S. P. Revision Committee and peroxide-free ether was used in the assays.

RESULTS.

TABLE I.

	R. E. Schoetzow, Gm. Alkaloids/100 cc.	L. D. Seif, Gm. Alkaloids/100 cc.
Method 1.	2.216	2.204
	2.209	...
Method 2.	2.343	2.003
Method 3.	2.251	...
Method 4.	2.155	2.213
	2.162	2.204

COLLABORATORS' COMMENTS.

R. E. Schoetzow: "We prefer Method 4 using paper as the absorbent. Method 1 requires too much time as it took more than a whole day to complete the analysis according to this method. A two-hour extraction with the mechanical extractor mentioned in Method 3 is not sufficient; about four and one-half hours were required for complete extraction of the alkaloid during this step."

L. D. Seif: "Method 1. No emulsion was formed when no water was added to the fluidextract, but a slight amount of water caused troublesome emulsions. Method 2. Emulsions also occurred in this hand-shake-out method. Method 3. The mechanical extractor did not extract all of the alkaloid in three hours. It was necessary to transfer to a separatory funnel and shake out by hand. Method 4. This method was found to be the least troublesome. Paper was used as the absorbent. One assay, using sawdust, gave slightly lower results."

A series of assays was then run, using ether which gave a positive test for peroxide when tested with cadmium potassium iodide. The results were low and did not check in duplicate assays, confirming the conclusions of other workers (6) that peroxide-free ether should be used in this assay. These results are given in Table II.

TABLE II.

	Ether Containing Peroxide Gm. Alkaloids/100 cc.	Peroxide-Free Ether Gm. Alkaloids/100 cc.
Method 1.	1.16	1.435
	1.29	1.425
Method 2.	1.06	1.396
Method 4.	1.13	1.42

These two series of assays indicated that Method 4 was satisfactory when peroxide-free ether was used, but there was some question as to what absorbents could be used since it had been shown by Morrison and Bliss (7) that sawdust retained a rather high percentage of certain alkaloids. Two series of assays were run using asbestos, paper, exhausted ipecac and sawdust as the absorbents. All the

absorbents were free from alkaloids when tested by the U. S. P. test for alkaloids in absorbents. The exhausted ipecac was used with the thought that it should give up all of the absorbed alkaloids rather easily and serve as a control on the other three absorbents. In one series the absorbents were impregnated with Fluidextract of Ipecac (of different manufacture than that previously reported) and in the other series with a solution containing a known amount of emetine hydrochloride. The results are given in Table III.

TABLE III.

	Fldext. Ipecac, Gm. Alkaloid/ 100 cc.	Solution Made to Contain 0.0755 Gm. Emetine (as Alkaloid) per 10 cc. Gm. Alkaloid/10 cc.
Sawdust absorbent	1.464	0.0711
	1.474	0.0680
Paper absorbent	1.55	0.0752
	1.53	0.0781
Asbestos	1.51	0.0762
		0.0772
Exhausted ipecac	1.522	0.0752
	1.541	0.0776
Straight ether shake-out		0.0752

These assays indicate that either asbestos or paper is a suitable absorbent and that while sawdust does not retain as great an amount of emetine as has been reported, when used with other alkaloids, still it gives low results and should not be used as an absorbent.

The results obtained in the three tables showed that the following method (Method 4) was the most practical method, that the results compare favorably with those of the present U. S. P. method and that uniform results could be secured in different laboratories when peroxide-free ether was used.

METHOD.

From a pipette measure 10.0 cc. of Fluidextract of Ipecac into an evaporating dish containing either absorbent paper or asbestos which gives no test for alkaloids when treated according to the U. S. P. method for absorbents. Dry at a temperature not exceeding 60° C. and transfer to a flask containing 100.0 cc. of peroxide-free ether. Stopper, shake well and allow to stand for five minutes. Then add 10 cc. of ammonia T.S. using a portion of the ammonia T.S. to rinse traces of absorbent from the evaporating dish. Stopper tightly and shake for one hour in a mechanical shaker or, occasionally, by hand for a period of about two hours. Allow the mixture to stand over night and again shake occasionally during a one-hour period. Allow the absorbent to settle and decant 50.0 cc. of the clear supernatant liquid into a separatory funnel. Completely extract the alkaloid from the ethereal solution with approximately normal sulphuric acid, using 15 cc. the first time and 10 cc. for each succeeding extraction, filtering each portion into a second separatory funnel. Extraction should be continued until no visible reaction is noted in the sulphuric acid solution when tested with mercuric potassium iodide, T.S.

To the combined acid solution add about an equal volume of peroxide-free ether, make alkaline with ammonia T.S. and extract with successive portions of ether until no visible reaction takes place when a few cc. are evaporated to dryness, dissolved in dilute sulphuric acid and tested with mercuric potassium iodide, T.S. Filter each portion into a 200-cc. flask and evaporate carefully on a steam-bath, nearly, but not quite to dryness. Add 5 cc. of ether and again evaporate nearly to dryness. Add 10.0 cc. of 0.1*N* sulphuric acid and heat on steam-bath to effect complete solution and to remove all of the ether. Cool, and titrate excess acid with 0.1*N* sodium hydroxide using methyl red indicator. Each cc. of 0.1*N* sulphuric acid corresponds to 0.0240 Gm. of ether-soluble alkaloids of ipecac.

Another sample of fluidextract was assayed by the collaborators by the above method using asbestos or paper as absorbents. The results on both the first and second samples are given in Table IV.

TABLE IV.

	Sample 1. Paper, Gm. Alkaloids/100 cc.	Sample 2. Paper, Gm. Alkaloids/100 cc.	Asbestos.
R. E. Schoetzow	2.162	1.532	1.50
		1.550	1.52
J. W. E. Harrisson			1.61
			1.56
L. D. Seif	2.213	1.55	1.51
	2.204	1.53	

The average of three assays on Sample 1 is 2.193 with a low of 2.162 (1.4%) and a high of 2.213 (0.91%).

The average of 9 assays on Sample 2 is 1.54 with a low of 1.50 (2.59%) and a high of 1.61 (4.56%).

CONCLUSIONS.

A practical method for Fluidextract of Ipecac is presented which does not yield troublesome emulsions, and by which uniform results may be secured by different analysts.

The value of peroxide-free ether for the assay and the retention of alkaloids by sawdust is confirmed.

REFERENCES.

(1) S. Palkin and H. R. Watkins, JOUR. A. PH. A., 13 (1924), 694.
(2) S. Palkin, A. G. Murray and H. R. Watkins, *Ind. Eng. Chem.*, 17 (1925), 612–614.
(3) A. R. Bliss, *J. O. A. C.*, 10 (1927), 359–362.
(4) E. Leger, *J. pharm. chim.*, 6 (1927), 501–505.
(5) The British Pharmacopœia 1932, page 175.
(6) L. E. Warren and W. T. McClosky, Report on the Assay Procedures for a Number of Drugs and Pharmaceutical Preparations, page 49.
(7) R. W. Morrison and A. R. Bliss, *Am. J. Pharm.*, 104 (1932), 590–593.

MISCIBLE FLUIDEXTRACT OF IPECAC.*

BY J. A. REESE AND W. G. CROCKETT.

The chief factors to be considered in the manufacture of fluidextract of ipecac are (1) the choice of a menstruum which will exhaust the drug and (2) the obtaining of a fluidextract which will mix with syrup to form a permanent syrup of ipecac. Seventy-three per cent alcohol is effective as a menstruum but produces a fluidextract which is not miscible with syrup. Thirty-seven per cent alcohol, as used in U. S. P. X, renders extraction difficult and does not remove the resins which cause clouding when the fluidextract is mixed with syrup.

A process has been suggested to Sub-Committee No. 11 of the Revision Committee of the U. S. P., wherein the drug is exhausted with 73% alcohol, the alcohol

* Section on Practical Pharmacy and Dispensing, A. PH. A., Madison meeting, 1933.