A PRELIMINARY STUDY OF TINCTURE OF CANTHARIDES.*

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INTRODUCTION.

To accord with the newly adopted international standards for tinctures of potent drugs, the U. S. Pharmacopœia VIII directed that 10 Gm. of cantharides be used in preparing 100 cc. of the tincture. This was twice the amount of drug used in the tincture previously official. Alcohol was directed to be used as the menstruum. Although no special investigation was made at the time of adoption, the practicability of a 10% tincture was soon questioned. The relative insolubility of cantharidin in alcohol (approximately 1–1333) indicated incomplete extraction. For many years, the official tincture and possible substitutes, therefore, have been under investigation.

Scoville (1) reported that the tincture of cantharides made by the official method represented but from $^1/_2$ to $^2/_3$ of the cantharidin content of the drug used and recommended the use of glacial acetic acid in the menstruum as an aid to extraction.

Eberhardt (2) found the official method inadequate and obtained relatively poor results with an acid-alcohol menstruum. He reported complete exhaustion of the drug by treating with caustic alkali and extracting with dilute alcohol but the resulting tincture was weak in vesicating power. A tincture which was actively vesicant and which fully represented the cantharidin content of the drug was obtained by treating the drug with glacial acetic acid and acetone and extracting with acetone.

Scoville (3) gave the results of further study of tincture of cantharides. Fifteen experimental tinctures were made, using mixtures of several solvents as menstrua. None of these experiments was successful in producing a tincture which fully represented the drug. Digestion, preliminary to percolation, was found to increase the yield of cantharidin. The use of glacial acetic acid in the menstruum was again recommended.

Scoville (4) reported eighteen experiments. One of these, made by digestion and maceration, and employing in succession, water acidulated with glacial acetic acid, chloroform and alcohol, produced complete exhaustion but the investigator was unable to duplicate his success when using other samples of cantharides. A mixture of glacial acetic acid and alcohol, 1 in 10, was again recommended as the most satisfactory menstruum.

Scoville (5) obtained approximately 90% exhaustion by extracting cantharides with glacial acetic acid and acetic ether in a Soxhlet apparatus, adjusting the volume with alcohol.

In 1919, Nitardy (6) used a menstruum of potassium hydroxide, water and alcohol suggested by Squibb (7) for the preparation of a fluidextract of cantharides. The tincture obtained was satisfactorily vesicant and contained 99 mg. cantharidin in 100 cc. The cantharidin content of the drug from which the tincture was made was not stated.

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In 1921, Nitardy (8) reported that wide variation in the results obtained from the use of a hydro-alcoholic menstruum containing potassium hydroxide prompted him to withdraw his recommendation of 1919.

As the result of a series of experiments in which he used chloroform, acetone and glacial acetic acid as aids to extraction, Nitardy (9) recommended the use of glacial acetic acid in the menstruum for the official tincture of cantharides.

In the U. S. Pharmacopœia X, the menstruum for tincture of cantharides was directed to be composed of 1 volume of glacial acetic acid and 19 volumes of alcohol. In the U. S. Pharmacopœia XI, this was increased to 1 volume of glacial acetic acid and 9 volumes of alcohol. Tincture of cantharides prepared by the present official method has a strong acetous odor; chiefly because of the odor, numerous objections to the present formula have been voiced.

Feeling that the work previously done on this subject, while valuable, was not conclusive, the writer undertook further investigation in the hope of devising a practical method which would yield a tincture of cantharides free from the objectionable features of the present official tincture.

EXPERIMENTAL.

Two lots of cantharides were procured and assayed by the U. S. P. method. Drug A, a fine powder, yielded 0.662% cantharidin. Drug B, a very fine powder, yielded 1.165% cantharidin.

Nine tinctures were prepared from Drug A and assayed according to Scoville's (3) modification of the method of Self and Greenish (10). The methods of preparation, menstrua used and assay results are shown in the following table:

TABLE I.

	Method.	Menstruum.	Cantharidin Content, Maximum—0.0622 Gm.	Percentage of Extraction.
1.	Percolation	Alcohol	0.0160 Gm.	25.7%
2.	Percolation	Alcohol + 2.0% CH_3COOH	0.0362 Gm.	58.2%
3.	Percolation	Alcohol + 4.0% CH_3COOH	0.0420 Gm.	67.5%
4.	Percolation	Alcohol + 7.0% CH_3COOH	0.0400 Gm.	64.2%
5.	Percolation	Alcohol + 10.0% CH_3COOH	0.0508 Gm.	81.7%
6.	Percolation	Alcohol + 0.5% HCl	0.0333 Gm.	53.5%
7.	Percolation	Alcohol + 1.0% HCl	0.0439 Gm.	70.7%
8.	Percolation	Alcohol + 1.5% HCl	0.0469 Gm.	75.4%
9.	Maceration	Alcohol + 1.0% HCl	0.0589 Gm.	94.7%

In an attempt to verify the favorable results obtained by the use of hydrochloric acid in the menstruum, four tinctures were prepared from Drug B and assayed in the same manner. The methods of preparation, menstrua used and assay results are shown in Table II.

TABLE II.

	Method.	Menstruum.	Cantharidin Content, Maximum—0.1165 Gm.	Percentage of Extraction.
1.	Percolation	Alcohol + 0.5% HCl	0.1056 Gm.	90.6%
2.	Percolation	Alcohol + 1.0% HCl	0.1043 Gm.	89.5%
3.	Percolation	Alcohol + 1.5% HCl	0.1026 Gm.	88.1%
4.	Maceration	Alcohol + 1.0% HCl	0.1126 Gm.	96.7%

In preparing the tinctures from Drug B, it was found necessary to mix three parts of purified sand with one part of the drug to facilitate the passage of the menstruum. No sand was used in the preparation of the tinctures from Drug A but it probably could have been used to advantage. The relatively low cantharidin content of tinctures 6, 7 and 8 may be due, in part, to the tendency of powdered cantharides to form masses through which the menstruum penetrates with difficulty. The assay result obtained in tincture 9 tends to confirm this view.

The method by which the tinctures were assayed, while it is perhaps the best yet devised, is long and tedious and considerable practice is necessary to develop the skill required for consistent results. It is recommended that an attempt be made to devise a method of volumetric assay.

SUMMARY.

1. Earlier investigators found that a 10% tincture of cantharides, extracted with alcohol, did not fully represent the drug from which made.

2. The present Pharmacopœia directs a menstruum of alcohol containing 10% of glacial acetic acid. This is objectionable in that the tincture so made has a strong acetous odor.

3. Experiments were conducted in an attempt to devise an alternate method.

4. Certain of these experiments tended to confirm the conclusions of earlier investigators regarding a menstruum of alcohol or of alcohol and glacial acetic acid.

5. Certain of the experiments indicate that a menstruum of alcohol containing $^1/_2$% to 1% of hydrochloric acid will yield a satisfactory tincture.

6. Maceration gave a higher percentage of extraction than did percolation.

CONCLUSIONS.

1. The use of 10% of glacial acetic acid in the menstruum for the official tincture of cantharides seems to be unwarranted.

2. A menstruum of alcohol containing $^1/_2$% to 1% of hydrochloric acid appears to yield a satisfactory tincture of cantharides.

3. Further study should be made to determine the minimum amount of hydrochloric acid necessary for complete extraction.

4. Maceration is superior to the official process of percolation as a method of extraction for cantharides.

ABSTRACT OF DISCUSSION.

William J. Husa remarked that the use of hydrochloric acid is important.

C. O. Lee inquired whether the author had found a satisfactory assay for the tincture. The author replied that this paper represented preliminary work.

REFERENCES.

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