

JOURNAL OF THE
TINCTURE OF CANTHARIDES.*

BY F. W. NITARDY.

The original and first five revisions of the U. S. P. directed the use of diluted alcohol as a menstruum for tincture of cantharides. In the sixth revision the menstruum was changed to alcohol. While the present menstruum has been the official one for nearly forty years, an examination of the tincture produced by the official formula will reveal that there is some room for improvement in the preparation. Various investigators, in fact, have found that alcohol is not a very good solvent for cantharidin or the oily constituents which probably are equally responsible with the cantharidin for the vesicant properties of the drug.

Some time ago the writer had various lots of Tinctures of Cantharides, obtained through the regular channels of trade from five well-known pharmaceutical manufacturing houses, examined, and found that they were practically inactive. As the assay for cantharidin is rather unsatisfactory, actual tests of the vesicant properties of the tinctures were employed instead and carried out as follows: The inner side of the forearm was carefully washed with soap and water and, thereafter, with diluted acetic acid; the tincture was applied to a space about $\frac{1}{2}$ " in diameter and the surface protected by fastening a crucible cover over the spot with a piece of adhesive tape. None of the tinctures examined produced a reddening of the skin. Fifty mils of each tincture were then evaporated spontaneously to a soft extract and the extract applied in the same manner. Only one of the extracts yielded a blister; the others produced but slight irritation.

These results led to an investigation and a review of the literature on this subject. The most notable article found was a paper by Dr. E. R. Squibb published in the Proceedings of the A. Ph. A. of 1871 (Vol. 19, page 457). In this article Dr. Squibb recommends the use of a hydro-alcoholic menstruum containing sufficient potassium hydroxide to combine with the cantharidin and saponify the oil present, for preparing a fluidextract. The paper goes into considerable detail and states that a very active preparation results from the process given.¹ Later R. Rother recommended the use of potassium hydroxide in the preparation of tincture.

In a discussion on the activity of potassium cantharidate by Dr. E. R. Squibb, Charles L. Eberle and others at the 1872 meeting of the American Pharmaceutical Association, some doubt was thrown on the activity of potassium combinations with the active principles of cantharides, but I found no further papers or records which cleared up the question. In a discussion of W. L. Scoville's paper on "Tincture of Cantharides" at the A. Ph. A. Convention in 1910, C. S. N. Hallberg recommended the use of potassium hydroxide in producing an active cantharides preparation.

To determine the value of potassium hydroxide in this connection a tincture was prepared by a method adapting the Squibb process for fluidextract of cantharides as outlined in Dr. E. R. Squibb's paper.² The tincture so obtained was

* Read before Section on Practical Pharmacy and Dispensing, A. Ph. A., New York meeting, 1919.

¹ *Proc. A. Ph. A.*, 25, p. 109.

² *Ibid.*, 19, p. 457.

tested for vesicating properties in the same manner as outlined above. It produced a nice blister in six hours, which indicated that the method would yield a satisfactory product. Further batches were then made, tested for vesicant properties and observed for a time to see if they would keep. All were found satisfactory and apparently stable. In fact, the product seemed so good that I feel justified in recommending the following formula as a substitute for the present official one.

TINCTURE OF CANTHARIDES.

Cantharides in No. 60 powder.....	100 Gm.
Potassium hydroxide.....	6.8 Gm.
Alcohol 7 volumes	} Sufficient quantity.....
Water 3 volumes	

To make, 1000 mls

Dissolve the potassium hydroxide in 300 mls of water and add it to the powdered cantharides. Mix well, then add 700 mls of alcohol and place the mixture in a well covered container. Allow to macerate for one week, stirring daily. Transfer it to a percolator which has previously been stoppered and after the drug has settled allow to percolate until all the tincture has drained from the drug. Then continue percolation with a menstruum consisting of alcohol 7 volumes, water 3 volumes until a total of 1000 mls of tincture has been obtained.

Description: One lot of tincture made by the above process was examined and gave the following constants:

Alcohol.....	65.45 percent
Extractive.....	3.04 Gm. per 100 mls
Free K O H.....	None
Cantharidin.....	0.099 Gm. in 100 mls

The tincture has a greenish brown color and soapy cantharidal odor. It is miscible with diluted alcohol, yields a slight precipitate when mixed with 95 percent alcohol, but the latter re-dissolves on standing over night. It will mix with an equal quantity of water with little or no cloudiness. As the finished preparation is neutral to litmus paper, there should be no objection to the use of potassium hydroxide in its preparation.

As tincture of cantharides is largely used in hair tonics, miscibility with preparations containing about 50 percent of alcohol is a very desirable property. The present U. S. P. tincture will make a clear mixture only with U. S. P. alcohol.

LABORATORIES OF
E. R. SQUIBB & SONS.

ABSTRACT OF DISCUSSION.

W. L. SCOVILLE: The question is whether adding potassium hydroxide in making a tincture of cantharides will always produce a vesicant preparation. I tried one tincture made that way but did not get a satisfactory preparation. In the first place, cantharidin is not an acid nor does it combine with alkalis in any definite proportion so far as I know. I have tried to titrate it but without success. If cantharidin combines with an alkali in any definite proportion, we should certainly be able to estimate it by titration. I notice that Mr. Nitardy's tincture of cantharides is neutral. This might be due to neutralization from a free organic acid that may be present in cantharides. I do not know if this is the case, but it should be an easy thing to prove. To my mind the only way to test tincture of cantharides fairly is to make a quantitative estimation of the cantharidin it contains. The fact that it will blister only shows that it has vesicating properties which are better than those of the U. S. P. tincture.

F. W. NITARDY: I stated the assay in my paper. The tincture contains ninety-nine milligrams of cantharidin in 100 mls of tincture.

W. L. SCOVILLE: Do you know how much of cantharidin was present in the free state, if any?

MR. NITARDY: It was not estimated with this point in view. We assumed that all existed in combined form.

The questions in my mind are, first, whether potassium cantharidate is really active; second, whether the alkali can be so adjusted as to always obtain a neutral tincture. It seems that the oil is likely to vary. In fact I did expect that the amount of alkali required would have to be varied with different lots of drugs, but practical experience so far has shown that no variation is necessary and the amount of alkali used is in accordance with that recommended by Doctor Squibb in 1871.

We have succeeded in making a tincture much more active than has been possible by any other method. I have never seen tincture of cantharides, except the one made by this formula, which will actually raise a blister. I believe the vesicating qualities of the tincture are due not only to its cantharidin content, but also to the oil present in cantharidin and which is rendered soluble by the use of KOH. I have given the formula with complete detail and hope others will try it and determine the quality of the preparation they obtain.

OTTO RAUBENHEIMER: There is no doubt that Mr. Nitardy's work is constructive and it may result in a change in the pharmacopoeial formula for this preparation. There is a question in my mind regarding Mr. Nitardy's suggestion and that is, Is tincture of cantharides supposed to be a vesicant? I have never heard of its being used as a vesicant.

W. L. SCOVILLE: The best solvent for cantharidin is acetone; the next best chloroform, the next acetic acid, then acetic ether. It is very slightly soluble in most solvents. I will agree with Mr. Nitardy that the U. S. P. process does not give a tincture which shows activity in any way. The question is, do we want a tincture which will present cantharidin in acid condition or in neutral or alkaline condition? The thing that surprises me is the activity that he obtains from a tincture made with an alkali. If its process will always yield an active tincture it is probably the easiest and most economical method for making it; otherwise we can make it by the use of acetic acid, acetic ether, chloroform, acetone or various other solvents.

F. W. NITARDY: I did not mean to leave the impression that it would not be possible to produce an active tincture of cantharides by some other means, but I did not like to use acetic acid in the proportion necessary, because I believed that the finished product would be too acid for practical purposes, nor did I like to use chloroform, ether, acetone or a similar solvent, because it would render the tincture less miscible with preparations containing water, such as hair tonics. The tincture offered is clearly miscible in any proportion with dilute alcohol preparations.

As to whether we expect tincture of cantharides to be vesicant or not, I do not believe that this is within the province of the pharmacist to decide; that is a question for the medical profession. Tincture of cantharides should represent the drug in the proportion in which it is used. That is, a liter of tincture should represent the total activity of 100 Gm. of cantharides.

GEORGE M. BERINGER: Tincture of cantharides is one of the puzzling problems of the Pharmacopoeia. The cantharidin content in the drug is very difficult to extract; the process of heating and macerating was adopted because it was believed that it yielded the best solution that could be obtained in an alcoholic menstruum. The use of acetone, chloroform, etc., to the extent in which it would be necessary to make a good tincture, did not seem practicable to the Revision Committee.

I am surprised that Mr. Nitardy's tincture assays so high; the assay for cantharidin is not an easy matter. I should like to see Mr. Nitardy's method tested out very thoroughly. I have made some experiments along that line myself but they were not entirely satisfactory and that is one of the reasons why they were not recommended for consideration in the previous Pharmacopoeia.

A MICROSCOPICAL METHOD FOR THE QUANTITATIVE DETERMINATION OF VEGETABLE ADULTERANTS.*

BY FANCHON HART.

The following method for the quantitative determination of vegetable adulterants is based upon the observation that the percentage of the various

* Read before Scientific Section, A. Ph. A., New York meeting, 1919.