A STUDY OF PRECIPITATION IN FLUIDEXTRACT OF UVA URSI IV.*[1]

THE CAUSE OF THE CRYSTALLINE PRECIPITATE IN FLUIDEXTRACT OF UVA URSI AND ITS PREVENTION.

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INTRODUCTION.

The identification of the crystalline precipitate which forms in the official fluidextract of uva ursi has been described in a preceding paper. The present paper deals with the probable cause and prevention of its formation. Any treatment that would yield a fluidextract having no precipitate, when such were the rule, naturally raises the question as to the effect upon the value of the finished product. This has led to numerous assays for arbutin, the chief active agent of uva ursi and its preparations.

PREVENTION OF THE PRECIPITATION IN FLUIDEXTRACT OF UVA URSI.

Ball (2) found that the amount of precipitate in fluidextract of uva ursi was greatly diminished, and its crystalline character changed, if the drug were subjected to the action of steam under pressure, for a time, prior to its percolation. His experiments, though not conclusive, were of sufficient interest to warrant repetition and further study. Our procedure and results are given here.

The drug, prior to extraction, was placed in an autoclave at five pounds pressure, corresponding to a temperature of 110°, for a period of thirty minutes, on each of three successive days. A fluidextract made from the drug treated in this manner precipitated only slightly, and the small amount of sediment which formed contained but very few of the crystals which are usually found in considerable quantity.

Fluidextracts which we have prepared from the heat-treated drug, after the manner described, have remained almost free from sediment after several months. The results of this treatment would seem to confirm our belief that the precipitate in fluidextracts of uva ursi is the result of the action of enzymes.

THE EFFECT OF HEAT UPON THE ARBUTIN IN UVA URSI.

Any means of prevention of the precipitate in the fluidextract would be of little value if the active constituent of the drug were altered or decomposed by it. For this reason it seemed that arbutin assays should be made upon the fluidextracts from the heat-treated drug.

Zechner (1) reported a method for the quantitative determination of arbutin. Grimme (3) offered a modification of Zechner's method. This assay is long and tedious but Tisher (1932), Ball (1933) and Parks (1936) have been able to obtain consistent results with it. The twelve assays of arbutin, which are summarized in Table I following, were made by a combined and modified method of Zechner and Grimme. Since our modification is but a slight variation from the procedures cited, it will not be given in detail.

From these results it will be seen that the arbutin content of a fluidextract made from the heat-treated drug is somewhat lower than that of the untreated drug

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TABLE I.

Sample Number. Each Is an Average of Six Assays.	Arbutin Content of 25 Cc. of Fluidextract. Official Fluidextract of Uva Ursi.	Fluidextract from Uva Ursi Which Had Been Subjected to the Autoclave.
1	2.0390 Gm.	1.8624 Gm.
2	1.9638 Gm.	1.8402 Gm.

of the same lot. However, the arbutin content of the modified fluidextract is but slightly decreased, while the product is much more elegant.

One of the objectives of this investigation was that of finding a way of preparing fluidextract of uva ursi which would not sediment upon standing and which, at the same time, would be therapeutically valuable. We believe that this has been accomplished.

EVIDENCES OF AN ENZYME IN FLUIDEXTRACT OF UVA URSI.

It has been stated that the presence of ellagic acid, as a precipitate in liquid extracts of tannin-bearing drugs, is due to the hydrolysis of ellagitannin by means of an enzyme. No such enzyme, however, has been isolated.

The fact that we were able to obtain a fluidextract of uva ursi, from a heat-treated drug, which did not yield the usual crystalline precipitate identified as ellagic acid, has led us to assume that an enzyme is the cause of precipitation in this preparation.

In support of the belief that the crystalline (ellagic acid) precipitate in the official fluidextract of uva ursi was due to the action of an enzyme, the following experiment was carried out.

Two hundred and fifty Gm. of uva ursi were heat-treated, as previously described, and extracted. The first 200 cc. of the percolate were set aside as the reserve percolate and labeled C. After five months no precipitation had occurred.

At this time two lots of 250 Gm. of uva ursi, untreated, were used to prepare the official fluidextract. The first 200 cc. of each was set aside as the reserve percolates, and labeled A, and B, respectively.

One hundred cc. of percolate C were then added to 100 cc. of each A and B percolates and well mixed. The remaining 100 cc. of each, A and B percolates, served as controls. After four months the four lots of fluidextract were filtered and the precipitates weighed. The results are given in Table II following.

TABLE II.

Sample.	Weight of Precipitate.
100 cc. Fluidextract A, + 100 cc. Fluidextract C	0.5254 Gm.
100 cc. Fluidextract A, Control	0.3366 Gm.
100 cc. Fluidextract B, + 100 cc. Fluidextract C	0.5031 Gm.
100 cc. Fluidextract B, Control	0.3611 Gm.

These results indicate that a fresh fluidextract, made from the untreated uva ursi leaves, contains some agent which, when added to a second fluidextract in which precipitation had been prevented, caused the latter to deposit the usual crystalline (ellagic acid) precipitate. This is, we believe, indicative of enzymatic action.

SUMMARY.

1. A method has been proposed for the manufacture of a Fluidextract of Uva Ursi in which the crystalline (ellagic acid) precipitate is prevented.

2. Experiments have been made which indicate that the crystalline (ellagic acid) precipitate in Fluidextract of Uva Ursi is due to enzyme activity.

REFERENCES.

(1) Zechner, L., *Pharm. Monatsh.*, 10, 169 (1929).
(2) Ball, J. E., Unpublished thesis, Purdue University (1933). (In this issue.)
(3) Grimme, C., *Pharm. Zentralh.*, 74, 669 (1933).

SOME NOTES ON THE TOLUENE MOISTURE DETERMINATION.*

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The determination of moisture by the toluene method was introduced into the eleventh revision of the United States Pharmacopœia for the first time. The purpose of this work is to compare the oven-drying method of moisture determination with the recommended procedure.

HISTORICAL.

The determination of moisture by distilling the sample with a liquid immiscible with water was first used by Marcusson in 1905 (1). Xylene was used as the immiscible liquid. Rogers (2) proposed the use of toluene to determine the moisture in leather. He used essentially the same procedure as that recommended by Marcusson. Dean and Stark (3) devised an apparatus in which the sample was refluxed with a liquid immiscible with water. The apparatus recommended in the eleventh revision of the U. S. P. is a modification of the Dean-Stark apparatus. Burns (4) used the xylene method in his work on the moisture content of aromatic drugs. Chow (5) found that the results of the xylene method were distinctly lower than those obtained by the oven-drying method. A number of investigators have used the distillation method with varying degrees of success. The collaborative work of Hoch and Prout on the moisture content of crude drugs led to the adoption of toluene as the immiscible liquid in the United States Pharmacopœia XI. They found that the one-hour distillation period recommended by Dean and Stark was not sufficient to obtain all of the moisture from ginger, acacia and asafœtida. The period of distillation is dependent upon the time required to remove all of the moisture from the crude drug.

EXPERIMENTAL.

A number of crude drugs were used in these experiments which had been purchased as official products. They were subjected to the oven-drying and the toluene distillation methods for moisture determination. The drugs selected were grouped into three main divisions, *First*, Drugs containing an official moisture standard; *Second*, Drugs which contained a volatile oil; and *Third*, Drugs containing resins. The drug was placed into an Erlenmeyer flask of 250–500

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