THE DETERMINATION OF ALCOHOL IN PHARMACEUTICAL LIQUIDS. II. A NEW METHOD.*

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In a previous paper (1) a study of the United States Pharmacopœia X and XI methods for the determination of alcohol in pharmaceutical liquids was described, with especial emphasis upon the procedures used in the presence of volatile substances other than alcohol and water. It was shown that these procedures consume much manipulative time and tend to give low results, and that a speedy, accurate method is badly needed.

The application of an apparatus similar to the Dean and Stark receiving flask (2), originally devised for the determination of water in petroleum and coal tar products, led to the development of a new procedure for alcohol assays. The alcohol, together with an immiscible solvent and water, is distilled from the sample and collected in a graduated receiver. Since the alcohol-water mixture and immiscible solvent are distilled together, there is a continual washing action. This entirely removes from the distillate such substances as are preferentially soluble in the immiscible solvent and which might otherwise interfere with the assay. This procedure gave uniformly accurate and reproducible results, especially striking in cases where the U. S. P. X and U. S. P. XI methods gave low results (1).

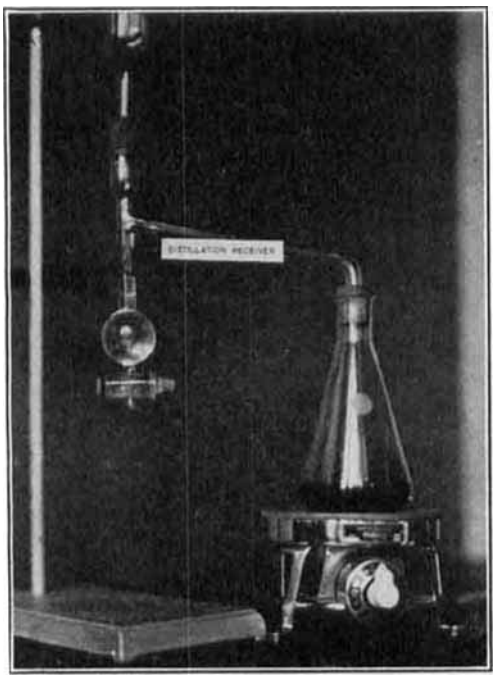

Fig. 1.—Distillation receiver.

EXPERIMENTAL.

The necessary apparatus consists of a 500-cc. Erlenmeyer flask, a condenser (the Hopkins type is best), an electric hotplate and a special distillation receiver. This distillation receiver is the only piece of special apparatus needed; it is simple and easily made and can now be obtained[2] under the name of "Merrell Alcohol Distillation Receiver." A round-bottomed flask and gas burner could be used instead of the Erlenmeyer flask and electric hotplate, but the latter is preferable from the viewpoint of safety.

The set-up of the apparatus, together with the appearance of the special distillation receiver, can be seen in the photograph. The measured sample, 50 cc. of water, and 25 cc. of heptane are put in the Erlenmeyer flask, the receiving flask filled almost to the 50-cc. mark with heptane and the apparatus connected.

Commercial heptane, boiling range approx. 90–100° C., is a satisfactory im-

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[1] From the Laboratories of The Wm. S. Merrell Co., Cincinnati, Ohio.

[2] The Wilkens-Anderson Co., Chicago, Illinois.

miscible solvent. It is cheap, has the proper boiling range and solubility behavior, and it carries the distillation along at a convenient speed. The expense connected with its use is slight since it can be recovered very easily and used repeatedly.

As a general rule, when it is suspected that the preparation to be tested contains less than 40% of alcohol, a 50-cc. sample should be used. If it is suspected that the liquid contains more than 40% of alcohol, or if the results of an assay carried out with a 50-cc. sample are over 42%, a 25-cc. sample should be used. This is in accordance with the conclusions reached in our previous paper on this subject. In some cases, where a relatively large quantity of an interfering contaminant is present, it is advisable to take 25 cc. or even only 10 cc. for the sample.

TABLE I.

Contaminant.	Sample of Known Alcohol.	Correct Alcohol Content.	Alcohol Content. U. S. P. XI Method.	Alcohol Content. New Method.
0.5 cc. Oils for F. E. Cascara Aromatic (anise, cinnamon, coriander, methyl salicylate)	50 cc.	17.5%	17.0% 16.7%	17.5% 17.4%
1 cc. Chloroform	50 cc.	17.5%	16.7% 16.6%	17.6% 17.4%
0.15 cc. Oils for Elixir Aromatic (orange, lemon, coriander, anise)	50 cc.	17.5%	17.1% 16.8%	17.5% 17.5%
1 cc. Chloroform	25 cc.	50.0%	49.1% 48.7%	50.0% 49.8%
1.5 Gm. Powdered Soap and 0.5 cc. Oil Rosemary (and excess sulfuric acid)	25 cc.	50.0%	49.4% 49.2%	50.0% 50.2%
None, but using the petroleum benzin shakeout in the U. S. P. XI method as if a contaminant were present	25 cc. 25 cc.	50.0% 77.8%	49.7% 77.2%	50.0% 77.7%
0.3 cc. Oils for Aromatic Spirit of Ammonia (lemon, lavender, myristica)	25 cc.	77.8%	76.2% 76.6%	77.7% 78.0%

It is advisable to shield the receiving flask from the heat of the hotplate with a square of asbestos. The distillation proceeds until the receiving flask contains about 48 cc. of alcoholic distillate; this usually takes from 30 to 45 minutes. The apparatus is disconnected and the distillate, which is usually rather warm, is cooled to the temperature at which the sample was measured before it is made up to exactly 50 cc. by dropping water into the flask. This temperature control is easily accomplished by having a large water-bath at room temperature in the laboratory. Samples and distillates can be quickly brought to room temperature by immersion in this bath and, if the body of water is large enough, no ordinary fluctuations in laboratory temperature will cause serious change in the temperature of the water during the course of the distillation. After the alcoholic distillate is made up to volume it is drained through the stop-cock into a dry container, separating the lighter immiscible solvent as would be done in a separatory funnel. The entire alcoholic distillate must be drained into a dry container and very thoroughly mixed; this is an important and necessary step. After thorough mixing, the specific gravity is determined in the usual way and by reference to

the proper tables the alcohol content can be found. Frequently the distillate is slightly hazy, presumably due to the suspension of minute droplets of heptane in the alcohol-water mixture. Upon standing over night these droplets will rise to the top, leaving a clear liquid; however, no significant difference could be detected when alcohol determinations were run before and after clearing, so that in practice it is not necessary to allow the liquid to clear.

Samples of known alcohol-water mixtures were contaminated with various volatile substances commonly found in official products and attempts were then made to determine the alcohol content of the original alcohols by the U. S. P. XI (4) method and this new method. The details of the procedures used are described in the previous paper (1) and in the above paragraph. The results of the U. S. P. XI assays, taken from the previous paper, will be repeated here in order to facilitate comparison.

DISCUSSION.

It can be seen that the new method consumes much less manipulative time than either the U. S. P. X or the U. S. P. XI method. This is especially true in the case of the U. S. P. X method, where a double distillation was required in addition to the shakeout. The new method requires no more manipulative time than a straight distillation; it entails no shakeout, no addition of saturated sodium chloride solution, and no double distillation. All common volatile contaminants of the type which the official procedure removes by shaking with petroleum benzin are automatically kept from interfering by this method. Free iodine, ammonia, acetic acid, glycerin and other substances requiring special treatment must be kept from interfering by the use of preliminary measures as described in the U. S. P. XI (4). Acetone, which is commonly used with alcohol in pharmaceutical preparations, will interfere in the assay and should first be removed as directed by Hoff and Macoun (3).

As shown in the table, the U. S. P. XI method gives results as much as 5% low, and apparently there is no definite relation between low results and certain particular contaminants. When no contaminant is present the results are only slightly low if the usual petroleum benzin shakeout is carried out just as if an interfering substance were there. This indicates that the shakeout does not completely remove all interfering substances, while contributing to the low results, and therefore a method which does not employ a shakeout, has no losses due to other causes, and which efficiently removes the interfering substances should give correct results. The new method accomplishes this result and at the same time it decreases the amount of manipulation required in the assay.

Coöperative assays of known alcohols with various contaminants have been carried out by six laboratories comparing this new method with the U. S. P. XI method. In a majority of cases the new method gave more accurate results than the U. S. P. XI method. The maximum deviations in the results of the six laboratories for each of four samples tested were in each case less with the new method than with the U. S. P. XI method.

SUMMARY.

A new method of distilling the alcohol from a pharmaceutical liquid for alcohol determination has been described, which gives more accurate results than hereto-

fore obtainable in the presence of volatile substances other than alcohol and water. The new method is not only more accurate, but is much less time consuming than previous methods.

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ANALYSIS OF GLYCEROPHOSPHATES.* I. DISCUSSION OF ASSAY METHODS FOR FERRIC GLYCEROPHOSPHATE AND MANGANESE GLYCEROPHOSPHATE.

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A.—FERRIC GLYCEROPHOSPHATE.

Ferric glycerophosphate is customarily assayed by reducing the ferric ion with hydriodic acid, the iodine liberated being determined by titration with standard sodium thiosulfate (1). This reduction proceeds but slowly and is reversible. To force the reaction to completion it is necessary to keep the concentration of ferric ion and of hydriodic acid as high as possible. Thus a distinct excess of mineral acid such as hydrochloric acid is required to prevent the hydrolysis of ferric chloride to ferric basic chloride. However, the mineral acid concentration must not be too high since it tends to form complexes with the ferric ion. This excess of acid serves also to increase the concentration of hydriodic acid, the source of which is usually potassium iodide. Oxygen must be absent from the solution since it reacts slowly with hydriodic acid to form iodine, thus giving high results. The reaction is far from instantaneous, various authors recommending reaction periods of from 5–60 minutes. The reaction velocity increases with increasing temperature, temperatures of as high as 60° C. having been recommended.

With solutions of pure ferric salts the speed of reaction is not a problem, Oakley and Krantz (2) having found that the reaction is rapid. With phosphates present Kolthoff (3) obtained low results unless the concentration of mineral acid was sufficiently high. Glycerophosphates behave in a similar fashion, reducing the reaction velocity by forming complexes with the ferric ion.

The National Formulary V recognized this fact by prescribing in the assay procedure for ferric glycerophosphate a reaction period of 30 minutes at a temperature of 40° C. Since, however, it provided no means of removal of oxygen from the solution, this procedure gave results high by as much as two per cent.

In the newly published National Formulary VI this assay procedure has been improved by eliminating oxygen, by increasing the concentration of potassium iodide and of ferric glycerophosphate and by decreasing the concentration of hydrochloric acid. These changes all serve to promote a more rapid reaction with less error from air oxidation. However, even under these revised conditions the reaction is far from instantaneous and the minimum five-minute reaction period

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