

TABLE II.—ANALYTICAL DATA ON SOLUTION OF PHYSIOLOGICAL SALTS

Bottle No.	Calcium Chloride Assay, Gm. (10 Cc. Aliquot)	Potassium Chloride Assay, Mg. (5 Cc. Aliquot)	Total Chlorides Assay, Gm. (10 Cc. Aliquot)	Depression Freezing Point, ° C.	p <sub>H</sub>
1	0.0343	1.54	0.0532	0.56	6.5
2	0.0341	1.53	0.0533	0.57	6.6
3	0.0354	1.54	0.0538	0.56	6.0
4	0.0337	1.53	0.0532	0.56	6.4
5	0.0343	1.56	0.0529	0.56	6.4

The addition of sodium bicarbonate was not deemed advisable because of its alkalinity. Buffer salts were considered but in all probability unnecessary as the p<sub>H</sub> of the solution is quite constant.

The sodium chloride suggested is of the U. S. P. grade. Comparative studies of several commonly used brands of the C.P. salt show that the U. S. P. standard was in most cases slightly alkaline whereas the C.P. standard was slightly acid. This sodium chloride alkalinity tends to combat the acidity found in all commercial samples of calcium chloride.

Concerning the calcium chloride used these observations revealed that all hydrates of calcium chloride (CaCl<sub>2</sub>; CaCl<sub>2</sub>·2H<sub>2</sub>O; CaCl<sub>2</sub>·6H<sub>2</sub>O) seemed to impart a slight acidity to the solution. The hydrated gave a lesser degree of acidity than the anhydrous salt. Of the two hydrates the dihydrate is the better.

The solution has been made isotonic with blood serum and the isotonicity checked cryoscopically and through its speed of hemolysis of red blood cells.

In the assay for the potassium salt seven different procedures were tried with consistently low results and a high percentage error. The method suggested by Brown, Robinson and Browning (3), however, if followed carefully will give consistent and accurate results.

In the consideration of the use of Ringer's Solution as a solvent for the various ampul solutions of the National Formulary, there are only two ampul solutions in the group that are hypotonic, namely, emetine hydrochloride and mercuric succinimide. The latter, however, is decomposed in the presence of sodium chloride giving ionizable mercury and could not, therefore, be made isotonic by the addition of Solution of Physiological Salts.

The emetine hydrochloride, however, may be adjusted to isotonicity by the addition of 28.2 cc. of Ringer's Solution per 100 cc. of solution. This isotonic emetine hydrochloride in Ringer's Solution was prepared and checked cryoscopically.

#### CONCLUSION

A formula and monograph for a Physiological Salts Solution as a solvent for parenteral use have been proposed for the National Formulary.

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## A Review of Tentative Changes in the Ampul Monographs of the National Formulary

By R. K. Snyder\* and E. N. Gathercoal

#### INTRODUCTION

The Special N. F. Committee on Ampuls and Tablets<sup>1</sup> had their first meeting in January 1936 and laid the foundation for the work that has been done since that time. The ampul monographs, including the general monograph, were to be studied in detail and desirable changes were to be recommended to the N. F. Committee. This work has been completed and is set forth in a tentative form in the Bulletin of the National Formulary Committee (1).

The laboratory work involved was begun in the N. F. Laboratory in Chicago and completed in the A. Ph. A. Laboratory in Washington. Collaboration on suggested assay methods was conducted in the Laboratories which the committee members represented. The results were discussed and decisions reached in the six semiannual meetings of the Committee (2).

#### GENERAL DISCUSSION

In a broad sense the work involved standards, methods of preparation, tests for identity and purity of the drugs used, methods of assay, sterilization procedures, and methods for testing the suitability of the glass containers.

To serve as a starting point a supply of the various official ampuls was obtained from each of five commercial houses.

The tests of identity and purity as listed in the monograph of each drug in the U. S.

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P. XI or N. F. VI were applied to these ampul solutions. It was found that practically all of the identity and purity tests could be performed on the chemicals in the solutions and yielded satisfactory results. There were a few tests, such as "moisture content," which obviously could not be used on a solution of the chemical or because another chemical was present which would vitiate the test.

The **official assays** were carried out on each commercial lot of each ampul solution and the results were carefully studied. It was apparent that some of these methods required modification or replacement to increase accuracy of the assay. The literature was reviewed and other assay methods were tried out. From these results certain assays were selected and collaborative work was done by the committee members. Of the revised assays presented later in the paper, only two can be considered as being new, the others are modifications of assays presented in the literature. It should be noted that the assays of similar ampul solutions were made identical, such as the calcium salt assays and the chloride and iodide assays.

The **directions for preparation of the ampul solutions** were also investigated to determine if they were satisfactory. Particular attention was paid to the oil suspensions in regard to smoothness, uniformity, particle size and any tendency for the particles to clump or aggregate.

The **testing of small and large glass containers** of ampul solutions has been discussed in previous papers (3) by the authors. After collaboration with chemists in the laboratories of glass manufacturers, as well as of ampul manufacturers, a method has been selected for ampuls up to 100-cc. capacity and a second method for containers of 100 cc. to 1000-cc. capacity. Further collaborative work is in progress at the present time to determine the effect on the surface durability of treated soft glass containers by aging common parenteral solutions in them.

It is of interest to note that no deletions of ampul monographs have been recommended, but that three new monographs

have been suggested and prepared. These are Ampuls of Bismuth and Potassium Tartrate in Oil, Ampuls of Sodium Salicylate and Iodide, and Ampuls of Sodium Salicylate and Iodide with Colchicine.

*Tests for Ampul Glass.*—The glass in ampuls of a capacity of 100 cc. or less shall meet the following test for solubility and reaction as a minimum requirement of quality:

Take a sufficient number of ampuls, not less than six, cleanse them thoroughly, rinse in distilled water and dry. Coarsely crush the dry ampuls, mix the crushed glass well, and reduce a sufficient quantity of it to a powder in a suitable steel mortar or mill. Sift the powdered glass and reserve the portion that will pass through a No. 40 standard mesh sieve, but will not pass through a No. 60 standard mesh sieve. Free this portion of glass from particles of steel with a magnet, wash it with alcohol to remove the finer dust particles and dry it in an oven. Place 10 Gm. of the dry glass, accurately weighed, in a resistance glass flask of about 125-cc. capacity, add 40 cc. of ampul water, loosely cap the flask with a glass or metallic cover, and autoclave for 30 minutes at 15 lbs. pressure (121° C.). Cool the autoclave to atmospheric pressure within 30 minutes, then remove the flask from the autoclave at once, cool rapidly to room temperature and titrate the contents of the flask with fiftieth-normal sulfuric acid, using phenol red  $p_H$  indicator. Also run a blank using the same kind of flask and cover and 40 cc. of ampul water from the same lot. Deduct the amount of fiftieth-normal sulfuric acid consumed in the blank from that consumed in the solution of the glass: the difference is not more than 0.75 cc.

Glass containers for solutions or suspensions intended for parenteral use and of a capacity greater than 100 cc. shall meet the following test:

Cleanse not less than six of the containers thoroughly with hot water and rinse them with distilled water. Nearly fill them with ampul water, invert Pyrex beakers over the openings of the containers, and autoclave them for 30 minutes at 15 lbs. pressure (121° C.). Cool the autoclave to about 100° C. within 30 minutes and then remove the containers from the autoclave at once. Transfer an accurately measured suitable quantity, but not less than 100 cc. from each container, to a pyrex beaker, acidify the solution with not more than 1 cc. of sulfuric acid, evaporate the solution to a volume of 30 to 40 cc. and carefully transfer the contents to a previously ignited, accurately weighed, platinum dish. Evaporate to dryness, ignite at a dull red heat until constant weight is obtained and express the total solids as parts per million of sulfates. In like manner determine the total solids as parts per million of sulfates, in the ampul water from the same lot as used in the test. Deduct the latter figure from the former: the difference is not more than 3.5 parts per million.

*Assay of Ampuls of Bismuth and Potassium Tar-*

*trate in Oil.*—Transfer an accurately measured volume of the uniform suspension containing about 0.2 Gm. of bismuth and potassium tartrate, to a crucible and add sufficient shredded filter paper to absorb the oil. Touch a flame to the oil-soaked paper, and when the mass is carbonized, ignite it. Cool, add nitric acid, cover the crucible with a watch glass and heat on a water-bath until the residue dissolves. Rinse the crucible into a filter and carefully wash the filter. Add stronger ammonia water to the filtrate until a slight but permanent precipitate is produced, then add 2 cc. of nitric acid and increase the volume to about 100 cc. Heat the solution to boiling and add 50 cc. of tenth-molar dibasic ammonium phosphate (also heated to boiling) slowly during the course of three minutes. Digest the mixture at 80° C. for one hour. Allow to settle and decant through an ignited, tared Gooch crucible, washing the precipitate three times with 50-cc. portions of hot water. Transfer the precipitate to the crucible with cold water, wash with cold water, dry and ignite the crucible to dull redness for a half-hour and weigh the bismuth phosphate,  $\text{BiPO}_4$ .

*Assay of Ampuls of Bismuth Subsalicylate.*—Transfer an accurately measured volume of the uniform suspension containing about 1 Gm. of bismuth subsalicylate, to a tared crucible. Add sufficient shredded ashless filter paper to absorb the suspension. Touch a flame to the oil-soaked paper, and when the mass is carbonized, ignite it. Cool, add 3 cc. of nitric acid, drop by drop, and warm until the residue is dissolved. Evaporate the solution to dryness, ignite the residue at red heat and weigh as  $\text{Bi}_2\text{O}_3$ .

*Assay of Ampuls of Calcium Chloride.*—Transfer an accurately measured volume of the ampul solution, containing about 0.25 Gm. of calcium chloride, to a beaker. Add 2 cc. of hydrochloric acid and 100 cc. of distilled water, heat to boiling, make alkaline with ammonia T.S., and add, with stirring, an excess of hot ammonium oxalate T.S. Heat the mixture on a water-bath for one hour, filter, and wash the precipitate on the filter with warm distilled water until the washings give no precipitate with calcium chloride T.S. Transfer the precipitate and filter to a beaker, add 100 cc. of distilled water and 10 cc. of sulfuric acid. Heat the solution to 70° C. and titrate with tenth-normal potassium permanganate.

Each cc. of tenth-normal potassium permanganate is equivalent to 0.005550 Gm. of  $\text{CaCl}_2$ .

*Assay of Ampuls of Calcium Gluconate.*—Transfer an accurately measured volume of the ampul solution, containing about 0.5 Gm. of calcium gluconate, to a beaker and proceed with the assay as directed under Ampuls of Calcium Chloride.

*Assay of Ampuls of Ephedrine Sulfate.*—Transfer an accurately measured volume of the ampul solution, containing about 0.25 Gm. of ephedrine sulfate, to a separatory funnel or a continuous extraction apparatus, add sufficient distilled water to make

about 10 cc. and then 3 cc. of half-normal sodium hydroxide and extract the alkaloid completely in the continuous extraction apparatus, or by shaking with six successive portions of ether using 20 cc., 15 cc., 10 cc., 10 cc., 10 cc. and 10 cc., respectively. Collect the ether extractions in a separatory funnel, wash the combined extractions with 5 cc. of distilled water and transfer the washings to a second separatory funnel. Extract the water washings with 10 cc. of ether and add this ether extraction to the combined ether extractions in the first separatory funnel. Discard the residual water. Extract combined ethereal solutions with 15 cc. of tenth-normal sulfuric acid, followed by 10 cc. and 5 cc. portions of distilled water. Collect these acid and water extractions in a beaker and gently evaporate on a water-bath until the odor of ether is no longer perceptible. Cool and titrate the excess acid with fiftieth-normal sodium hydroxide using methyl red T.S. as the indicator.

Each cc. of tenth-normal sulfuric acid is equivalent to 0.01651 Gm. of  $\text{C}_{16}\text{H}_{18}\text{ON}$ .

*Assay of Ampuls of Green Iron and Ammonium Citrates.*—Transfer an accurately measured volume of the ampul solution containing about 1 Gm. of Green Iron and Ammonium Citrates, to a glass-stoppered separatory funnel, add ammonia water to render alkaline and extract the alkaloid by shaking with three portions of chloroform. Wash the combined chloroformic extracts once with distilled water, add the washing to the alkaline liquid in a glass-stoppered flask, neutralize it with hydrochloric acid and add an excess of 5 cc. of acid; dilute with distilled water, if necessary, to make 25 cc.; then add 4 Gm. of potassium iodide and stopper the flask securely. Allow the mixture to stand for from twenty to thirty minutes; then add 50 cc. of distilled water and titrate the liberated iodine with tenth-normal sodium thiosulfate, using starch T.S. as the indicator.

Each cc. of tenth-normal sodium thiosulfate is equivalent to 0.005584 Gm. of Fe.

*Assay of Ampuls of Mercuric Salicylate.*—Transfer an accurately measured volume of the suspension, containing about 0.3 Gm. of mercuric salicylate, to a prepared Gooch filter and wash with purified petroleum benzin to remove all of the oil. Place the Gooch filter and residue into a suitable flask and add 15 cc. of sulfuric acid and 15 cc. of nitric acid. Insert a small funnel in the neck of the flask and heat upon a sand-bath until the mixture is decolorized. Cool the solution, dilute it with 150 cc. of distilled water, add 2 cc. of ferric ammonium sulfate T.S. and titrate with tenth-normal ammonium thiocyanate.

Each cc. of tenth-normal ammonium thiocyanate is equivalent to 0.01003 Gm. of Hg.

*Assay of Ampuls of Sodium Chloride.*—Transfer an accurately measured volume of the ampul solution, suitably diluted with distilled water and containing about 0.15 Gm. of sodium chloride, to a casserole, add 200 cc. of distilled water and 10 drops

of dichlorofluorescein indicator. Titrate the mixture with tenth-normal silver nitrate solution until the silver chloride flocculates and the mixture turns to a faint pink.

*Assay of Ampuls of Sodium Iodide.*—Transfer an accurately measured volume of the ampul solution, containing about 0.25 Gm. of sodium iodide, to a casserole, add 200 cc. of the distilled water and 10 drops of dichlorofluorescein indicator. Titrate the mixture with tenth-normal silver nitrate solution until the silver iodide flocculates and the mixture turns a faint pink.

Each cc. of tenth-normal silver nitrate is equivalent to 0.01499 Gm. of NaI.

*Assay of Ampuls of Sodium Salicylate.*—Transfer an accurately measured volume of the ampul solution, containing about 0.25 Gm. of sodium salicylate, to a 100-cc. glass-stoppered cylinder and add 75 cc. of ether and 5 drops of bromphenol blue T.S. as the indicator. Titrate the mixture with tenth-normal hydrochloric acid, mixing intimately the aqueous and ethereal layers by vigorous shaking, until a permanent pale green color is produced in the aqueous layer.

Each cc. of tenth-normal hydrochloric acid is equivalent to 0.01601 Gm. of  $C_6H_4(OH).COONa$ .

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## Determination of Acetone

By Melvin W. Green\*

#### INTRODUCTION

Three methods are in general use for the determination of acetone. The official method depends upon the conversion of the acetone to iodoform with an excess of iodine and the subsequent determination of the iodine with thiosulfate. Another method makes use of the qualitative test for acetone in which the acetone is pre-

cipitated as a yellow mercury complex. The mercury in this complex is then determined mercurimetrically or gravimetrically. The third method takes advantage of the carbonyl group which reacts with hydroxylamine hydrochloride to form acetoxime, liberating hydrochloric acid which is titrated with alkali.

Since there has been some criticism of the present Pharmacopœial method, a comparison of the three methods was undertaken by this laboratory.

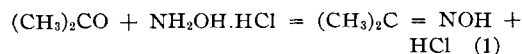
#### EXPERIMENTAL

*Purification of Sample.*—A commercial acetone, alleged to be of U. S. P. grade, was refluxed for two hours with calcium oxide and then fractionally distilled, collecting only that fraction which boiled at 56.3 to 56.4° C. (uncor.).

*Mercurimetric Method.*—In 1926, Jonescu-Matin (1) recommended the determination of acetone, as well as certain alkaloids, by forming the mercury complex and then determining the mercury contained therein.

The reagent was prepared by mixing 50 Gm. of mercuric oxide with 500 Gm. of concentrated sulfuric acid and then diluting to one liter with water. In conducting the test, 1 to 10 cc. of a 5% aqueous acetone were refluxed for twenty minutes in the presence of 10 cc. of 50% sulfuric acid, 10 cc. of the mercury reagent and enough water to make a total of 100 cc. The material in the flask was then cooled, filtered, washed with 100 cc. of water in divided portions, the residue washed into a flask by a stream of water from a wash bottle and digested with 25 cc. of a mixture of two parts sulfuric acid to one part of nitric acid until solution was effected. The mercury was then determined by the familiar thiocyanate method, using ferric alum as the indicator. Jonescu-Matin claims the complex to have the formula  $Hg_2SO_4 \cdot 3HgO \cdot 4(CH_3)_2CO$ . This would correspond to an acetone content of nearly 17%. However, the author experienced a higher and variable result, so variable that the method was abandoned as too unpredictable and too time-consuming for practicality.

*Oxime Method.*—In the oxime method, advantage is taken of the reactivity of the carbonyl group with hydroxylamine hydrochloride according to the following equation:



The HCl thus liberated may be titrated with 0.1N NaOH using methyl orange as an indicator, although various other single and a few mixed indicators have been advocated. However, according to Morasco (2) the reaction is only 94.4% complete.

The reaction was conducted as follows: Approximately 2 cc. of the purified acetone were added by

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