

SUGGESTIONS FOR IMPROVEMENT OF U. S. P. ASSAY PROCESSES.*

BY FRANTZ F. BERG.

The Pharmacopoeia is now used by a great many chemists in various industrial enterprises for the control of materials purchased on U. S. P. specifications or for purpose of determining the quality of a finished product.

Many of the tests and assay processes of the Pharmacopoeia as now laid down are designed for use by a pharmacist, and the equipment and wording of tests are governed by this assumption. These methods of assay are used to a larger extent by the chemist in a well-equipped laboratory, who might on many occasions use a slight modification as a time-saver and procure in many cases more accurate results. The methods as set forth by the U. S. P. are necessarily official, and in view of this fact the chemist so situated must often carry out a process which he could do quicker and better in another way.

In many cases this condition could be remedied by allowing an alternative method or an alternative piece of apparatus, which would not in any way be detrimental to the book as a legal standard.

The Pharmacopoeia contains some preparations for which no assay processes are appended but which are required to meet certain standards in various states, or as in the case with Solution Cresol Compound by the Insecticide Act it is required to bear a statement as to water content. A dispute may often arise where the analyses of such preparations are made by different methods. If the Pharmacopoeia is to continue as a legal standard it would be desirable to include methods of assay for ammonia content in Aromatic Spirit of Ammonia, water in Compound Solution of Cresol, an assay for flicin in Oleoresin of Aspidium and assay for Hexamethylamine. Some of the tests give rise to various interpretations, and cause confusion, owing to varied construction which may be placed on such phrases as absence of and presence of, when placed in parenthesis after a test which may be taken to mean an impurity, or absence of such impurity.

The following suggestions and criticisms are offered for improvement of the assay processes of the forthcoming Pharmacopoeia:

SUBSTITUTE FOR OAK SAWDUST IN THE ASSAYS OF FLUIDEXTRACT OF IPECAC AND FLUIDEXTRACT OF CINCHONA.

It has been my experience on many occasions that a source of oak sawdust was not at hand, and could not be procured without considerable delay. It was this condition which caused me to cast about for some other media as an absorbent.

The material which first suggested itself as a substitute was acid washed neutral asbestos fiber such as is used in preparing filter mats for Gooch crucibles. This material can always be found in the market, and requires less time to purify than does sawdust, or in the case of chemical laboratories asbestos is always on hand in purified state. After some experimentation the following modification of the U. S. P. assay for Fluidextract of Ipecac was found to give concordant and reliable results.

*Read before Scientific Section, A. Ph. A., City of Washington meeting, 1920.

From a pipette drop 10 mils of fluidextract of ipecac evenly over the surface of 2 Gm. of thoroughly washed neutral dry asbestos. Evaporate to dryness at a temperature not exceeding 80° C. Transfer the impregnated asbestos to a 250 mil flask, add 100 mils of ether. Rinse the dish, in which the mixture was evaporated, with 6 mils of ammonia water diluted with an equal volume of water (using a glass rod to remove any fibers that adhere too firmly to dish), add this to the flask, stopper the flask and shake it vigorously every few minutes for two hours. After the asbestos has subsided, decant 50 mils of the ethereal solution, representing 5 mils of the fluidextract. Completely extract the alkaloids from this solution by repeatedly shaking out with weak sulphuric acid. Collect the acid washings in a separator, add ammonia water until the solution is decidedly alkaline to litmus, and completely extract the alkaloids by repeatedly shaking out with ether. Evaporate the combined ether washings to dryness at a temperature not exceeding 60° C. Dissolve the alkaloid in 10 mils of tenth normal sulphuric acid V. S. and titrate excess of acid with fiftieth normal potassium hydroxide V. S., cochineal or methyl red being used as indicator. Each mil of tenth normal sulphuric acid V. S. consumed corresponds to 24 milligrammes of alkaloids of ipecac.

With asbestos it was found unnecessary to add the usual 10 or 15 Cc. water to cause balling of the mass before decanting an aliquot portion, thus a possible source of error is eliminated.

The temperatures stated in the above method should be included in assay, as it has been shown that ipecac alkaloids are prone to decomposition at higher temperatures.

This method may be applied equally well to Fluidextract of Cinchona.

COCAINE HYDROCHLORIDE.

The present Pharmacopoeia does not give a purity rubric for this chemical, with the consequence that a product varying in purity is found in the market.

The valuation of this chemical is, however, often carried out, either by assay or by determination of the melting point. In the former case it may be assayed either by shaking out with immiscible solvents or by direct titration with tenth normal silver nitrate V. S.

Depending upon whether chloroform or ether be used as an immiscible solvent, the results obtained are variable, and confusion often arises which could be avoided if an official method was provided.

The melting point of this chemical is also often disputed. The Pharmacopoeia gives the melting point between 183° C.-191° C., while it is held by some that pure Cocaine Hydrochloride has a melting point nearer 200° C.

It has been found that considerable variation of the melting point may be due to¹ manner in which this is determined, a long constant heat giving a much lower melting point than that found when material is introduced after a temperature within a few degrees of the accepted melting point is first obtained.

For the above reasons it would seem desirable that the new Pharmacopoeia establish an official assay process and determine whether or not the present melting point is correct.

CRESOL.

Under the description of this chemical is found a statement that it is soluble, one mil in about 50 mils of water usually forming a cloudy solution. This statement is very elastic and might be stretched to cover the present trade article,

¹ *Chem. Abstracts*, Vol. XIII, 22, p. 2971.

but if it be applied rigidly it is found that it is not soluble in 50 mils, and only in rare instances is a sample found to be soluble in 100 mils of water.

In the same monograph a statement is made that a solution of 1 mil of cresol in 60 mils of water is not more than slightly turbid, which is obviously incorrect if we are first unable to dissolve 1 mil cresol in 100 mils of water.

It seems that these tests are not correct indexes of the purity of present day product, and if these are too high, should be changed.

SOLUTION CRESOL COMPOUND.

The Insecticide Act provides that this preparation must bear a statement as to content of inert ingredients, principally confined to water, for which a process of assay should be appended.

The following process as recommended by W. W. Davies (JOURNAL A. PH. A. Vol. VI, p. 880), has been found to give reliable and concordant results.

By distillation of the solution with an equal volume of xylol through a dry condenser and collecting the distillate in a graduated cylinder, the water content may be read off directly.

TEST FOR METHYL ALCOHOL IN ETHYL ALCOHOL.

The present method for detection of methyl alcohol in ethyl alcohol is not satisfactory; in many cases a positive reaction is obtained, when applied to an alcohol of known purity.

Any one of several well-known tests for this impurity might be substituted for this test with better results, or the present test might be revised, bearing in mind that purity of fuchsin used may be one of the disturbing factors.

Much of the fuchsin now in the market is not pure. The writer has found samples of this chemical to contain in one case 85% sugar and in another case 50% of sodium chloride.

COPAIBA.

Under the tests for this oleoresin the statement is made, that, "after heating and the volatile oil has been driven off, a hard and brittle resin remains," which would seem to indicate that, if such a brittle mass was not obtained, it was not true specimen, when, as a matter of fact, several samples of accepted article yield a semi-solid resinous mass.

Another test under this oleoresin states, that "3 or 4 drops of volatile oil obtained by distillation with steam, when dissolved in 3 mils of glacial acetic and to which is added one drop of sodium nitrite T. S., and underlaid with 2 mils of sulphuric acid, shall not give a pink coloration to the acetic layer, indicating absence of Gurjun balsam."

This test is not reliable and often the pure article gives a positive reaction for this impurity.

OLEORESIN OF ASPIDIUM.

The quality and strength of this preparation is subject to considerable variation. Samples have been found to assay from 8% to 26% of filicin or filicic acid. Such a condition may be attributed to the fact that no assay is required for it.

The preparation is, however, often assayed by one of several methods; possibly the most used method is that of the Swiss Pharmacopoeia, which gives a fairly reliable index to crude filicic acid content.

Whether or not this method is a true index to its quality, or whether an assay for pure filicic acid should be devised, the writer is not prepared to state, but it would seem desirable to have a standard for this preparation, in order to secure a more reliable product.

ASSAY OF OPIUM AND ITS PREPARATIONS.

The present U. S. P. directions for assay read: Collect morphine crystals on a pledget of cotton in the neck of funnel.

In many cases the crystals obtained are so small that they pass through cotton and are lost, and the results vitiated.

A substitute for cotton is offered in the form of an Alundum or Gooch crucible; with the aid of suction either will retain all of the precipitate. By this method the morphine crystals may be weighed, thus providing a check on the volumetric titration.

A porous crucible of this type is even more suitable than filter paper, which is liable to rupture if suction is used. This is quite necessary when a slower filtering medium than cotton is used, else the rapid evaporation of ether leaves behind some of ether-soluble alkaloids, which would, of course, give higher results.

ABSTRACT OF DISCUSSION.

J. P. Snyder has used the method of Lyman F. Kebler for assaying Aromatic Spirit of Ammonia, with success. (See p. 615, July, 1917, THIS JOURNAL.—Editor.)

L. E. Warren regretted that the Pharmacopoeia gave the melting point for any of the alkaloids, because this is not definite for any of them.

Responding to a question of Arno Viehovever relative to Mr. Berg's view relative to assay of opium, the latter stated that his views coincided with those of H. W. Jones. (See January, 1920, JOURNAL A. PH. A., p. 51.) The use of filter paper is not satisfactory, owing to the slow filtration, he said. L. F. Kebler opposed the use of oak sawdust, he had found sand much more satisfactory. He contended that Mr. Berg's criticism of the assay of copaiba was not well taken, that it was almost impossible to obtain pure copaiba at present.

E. H. Grant stated that there was now very little, if any, copaiba imported, which would meet all the requirements of the United States Pharmacopoeia.

Mr. Berg stated that the sample of copaiba used in his work was passed by the Bureau of Chemistry. But that did not necessarily mean that they had erred—as he realized that they must often admit samples such as this which it is impossible to obtain in absolute purity. Mr. Kebler's correction as to quality of commercial Balsam Copaiba is accepted.

ASSAY OF AROMATIC SULPHURIC ACID.*

BY E. F. KELLY AND J. C. KRANTZ, JR.

Having occasion recently to examine a commercial sample of Aromatic Sulphuric Acid, the writers employed the method suggested in an article published in 1916 by the Maryland State Board of Health. This article criticized the Pharmacopoeial method of assay on the ground that the boiling for six hours of the water and acid mixture in a flask connected with a reflux condenser prevented the decomposition of the acid ethyl sulphate through the constant return of the alcohol to the solution instead of its removal. The modification suggested was to heat the mixture of aromatic sulphuric acid and water in an open beaker on a water-bath from three and a half to four hours. By this method, three assays

*Read before Section on Practical Pharmacy and Dispensing, A. Ph. A., City of Washington meeting, 1920.