allylisothiocyanate, and as this boils at 151° it will be found in the first fraction of the oil and will be recognized by its pungent odor.

After completing the examination of the volatile portion of a preparation it is often impossible to say whether some of the compounds found were used in the pure form or as ingredients of volatile oils. This is especially true of compounds such as camphor, thymol, menthol, or cineol which are often used in medicinal preparations.

For the guidance of the analyst in determining from his results what volatile oils are probably present, a list of the oils of the Pharmacopoeia, with their characteristic ingredients, is given.

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THE ANALYSIS OF PROPRIETARY MEDICINES.

AN OUTLINE.

BY W. S. HUBBARD.

For the examination of secret remedies there is not available any comprehensive work corresponding to the many good books on the subject of food analysis.

The number of substances which may be found in any mixture and the almost unlimited range of possibilities in the way of combinations of materials in different preparations sold for the same purpose makes it impossible to give any rigid procedure for the examination of such products. Nevertheless, certain tests and methods of examination which have been found useful can be described. The suggestions here presented were arranged primarily for the use of analysts in the Bureau of Chemistry who might have occasion to examine secret preparations sold for the treatment of various diseases.

There are certain determinations in the analysis of preparations of drugs which should always be made and other determinations which may be desirable, depending upon the medicinal claims or the use to which the preparation is to be put. Certain substances are very likely to be found in any such preparations, regardless of the use for which they are recommended. Suggestions as to the probable active constituents may be obtained by consulting the "Index to Diseases" in some Dispensatory or Materia Medica. When possible, tests should be made for each drug so mentioned. The absence of a drug generally used in treatment of conditions for which the remedy is recommended is often as important to establish as its presence. Very often by referring to "*Die Pflanzenstoffe*," Wehmer (1911), or to articles appearing more recently in the journals, it will be found that there are substances characteristic of certain drugs for which tests may be made. The finding of a certain ingredient does not always prove that a particular drug is present, but the absence of this ingredient will show the absence of the drug. This fact is very important when considering the medicinal claims. Of course account must be taken of any change this ingredient could undergo during manufacture. Bearing in mind the limitations mentioned, the following outline is offered as a general guide for the examination of proprietary medicines:

LIQUID PREPARATIONS.

The tests and determinations which should be made in all cases are:

Preliminary tests	Alcohols
Non-volatile matter	Emodin
Ash	Gums
Sugars	Resins
Glycerol	Color substances
Chloroform extract from acid solution	Volatile oils
Chloroform extract from alkaline solution	Inorganic material

Preliminary Tests.—The odor and taste of the preparation should be tested first, since these often help in the identification of the ingredients. A test should be made to ascertain the reaction, whether alkaline, acid or neutral.

Non-Volatile Matter.—The non-volatile matter or total solids should be determined preferably in a silica or well-glazed porcelain dish. In medicinal preparations substances which attack platinum are often present and some organic phosphorus compounds are always present in plant material and when ashed may attack a platinum dish. For the majority of preparations it is best to conduct the evaporation at or near 70° C. *in vacuo*.[1] Choose the amount of material so that the final weight of solids will be about 0.5 Gm. Dry to constant weight. With certain materials present it is practically impossible to obtain a constant weight and especially is this true of glycerol. When preparations contain large amounts of sugars it is best to evaporate to a syrupy consistency before putting in the vacuum oven. In some cases it is advisable to mix with sand. The sum of the non-volatile ingredients quantitatively determined should equal the amount of non-volatile material originally found. It is not always possible to secure an exact agreement between these figures, but an attempt should be made to approximate it as nearly as possible.

Ash.—The determination of ash is quite essential and very valuable in most instances if carried out properly. The method used in obtaining an ash depends upon the end in view and, therefore, varies with different products. The United States Pharmacopoeia, 9th Edition, page 589, describes a method of obtaining ash and it is the method which should be used in pharmaceutical preparations. A plant ash will be alkaline and usually contain small amounts of iron, sodium, potassium, and calcium salts, phosphates and chlorides with traces of magnesium and aluminum salts and silica. The degree of alkalinity is quite often of importance to determine whether alkalinity is due to plant material or to an added substance, either organic or inorganic. The original substance may be alkaline, a fact which should have been determined in the preliminary examination. When the ash is above 1 percent it is well to make quantitative determinations of the principal ingredients. Qualitative tests for the constituents should always be made no matter how small the amount of ash.

Sugars.—It is safe to say that a majority of the preparations contain some sugar. The methods used are those of *Bur. Chem. Bull.* 107[2] except that a definite volume may be taken. The sugars should be determined by means of the polariscope as well as gravimetrically.

Glycerol.—Glycerol may usually be detected by the behavior of the non-volatile matter. The best qualitative tests for the identification of glycerol are those of M. G. Denigés.[3] The quantitative method for wines[4] is generally ap-

plicable to medicinal preparations. A duplicate determination is made and after weighing is made up to definite volume and determined with the immersion refractometer and reference to Wagner's "*Tabellen Zum Eintauch-Refractometer*," Sondershausen (1907).

Alcohol.—The determination of alcohol must be carried out with care, since medicinal preparations usually contain a great variety of substances. The official method is that of the United States Pharmacopoeia, 9th ed., 592. The specific gravity determination should be supplemented with one made with the immersion refractometer to prove the presence or absence of methyl alcohol.[5]

Acid Chloroform Extract.—The alcohol is evaporated from a quantity of the preparation by heating on a water bath and the residue placed in a separatory funnel. It is made distinctly acid with normal sulphuric acid, shaken out several times with chloroform, using about 25 Cc. the first time and less the succeeding times. Most of the chloroform is distilled off, the remainder is transferred to a beaker and evaporated to dryness on a water bath. If any considerable amount of material is extracted it is well to purify by dissolving the residue in water and shaking out again. In some cases it is desirable to substitute ether for chloroform since some phenols are more soluble in this solvent. Caffeine, berberine, hydrastine, antipyrin, acetanilid, phenacetin, salicylic acid, benzoic acid, salol, phenol, cresols, guaiacol, and hexamethyleneamine are among the more important substances extracted by chloroform. Phenacetin, phenol, cresols, guaiacol, and salol are very slightly soluble in water. Phenacetin and salol are very seldom found in liquid preparations. For the estimations of caffeine, antipyrin and some of the other more common synthetic drugs, the work of W. O. Emery[6] and his co-workers should be consulted.

Alkaline Chloroform Extraction.—The original material which has been made acid and extracted with chloroform is now made alkaline with ammonia and again extracted with chloroform, using the procedure as described in the acid extraction. A second purification is necessary and sometimes even a third or fourth. After all extractions are made, the chloroform must be washed two or three times with water. When cocaine is present, ether, petroleum ether, or benzene is preferable to chloroform and care must be taken not to hydrolyze the cocaine. The purified material is dissolved in a very slight amount of 0.5 *N* or 0.1 *N* sulphuric acid and tested for alkaloids with Wagner's, Mayer's, picric acid, phosphomolybdic acid and other alkaloidal test solutions. Wagner's and Mayer's reagents are the most common, and while either precipitates nearly all of the alkaloids it sometimes happens that the quantity of alkaloids present is very small and the precipitate with Wagner's or Mayer's reagents is so slight that it may be overlooked, while some other reagent may give a precipitate which is quite distinct. It should be remembered that morphine may not be found here since it is only very slightly soluble in chloroform. Berberine and hydrastine may come out here as well as in the extract from the acid solution. Care must be used in the extraction of alkaloids since a number are easily destroyed by heat, or by excesses of acids or alkalies.

Emodin.—Since it is estimated that at least 50 percent of the nostrums contain a vegetable cathartic it is important that a test be made for them.[7]

Gums.—If the preparation contains much alcohol there cannot be any con-

siderable amount of gum present. To one or two cc. of material add alcohol. Any precipitate formed should be filtered off, washed with alcohol, dissolved in the smallest quantity of water possible and reprecipitated with absolute alcohol. From the nature of the precipitate it is usually possible to distinguish a gum. An article by L. A. Congdon[8] is helpful in many instances.

Resins.—If the material is an aqueous solution, then it can not contain much resin. To one or two cubic centimeters of material add water until there is no further precipitation. Wash the precipitate with water, dissolve in a small quantity of absolute alcohol and reprecipitate with water.

Coloring Material.—The coloring material most frequently met with in nostrums is caramel. This is identified according to the method of Amthor.[9] Alkanet, cudbear, cochineal and carmine are also frequently found in this class of preparations.

Inorganic Material.—The inorganic material can be determined in the ash in many cases. It is well in making qualitative tests to run the material through the group separations.

Arsenic.—The Gutzeit test is usually used in qualitative work.[10] A very rapid and accurate quantitative method in which arsin is passed into a solution of mercuric chloride and the resulting calomel weighed, is that of Claude R. Smith.[11]

Antimony.—Some of the material is made acid with hydrochloric acid, a platinum strip is placed in the solution and on top of this is placed a piece of pure zinc, forming a platinum-zinc couple. Any good text on qualitative analysis will give this method in more detail. It is well to carry on another test to which has been added a very small amount of antimony, say the minimum dose of tartar emetic, and also a blank with the reagent. The test is very sensitive and may be carried out in the presence of large amounts of organic material.

Volatile Oil.—If volatile oils or other volatile materials are present they can usually be detected during the determination of alcohol either by the odor or color of the distillate, which in some cases has a milky appearance. When volatile oils are present in considerable quantity or it is of importance that their identity be known, the method* of Alfred Hoffman[12] is helpful rather than such large works as Gildemeister[13] and Hoffman.

POWDERS, PILLS AND TABLETS.

Determination of, separation of, or tests for the following are made:

Preliminary tests	Chloroform extract from acid solution
Coating	Chloroform extract from alkaline solution
Non-volatile material	Emodin
Ash	Gums
Sugars	Resins

INORGANIC MATERIAL.

Preliminary Tests.—The preliminary tests given under Liquid Preparations should be supplemented in the case of powders, pills and tablets by grinding to a fine powder and examining under a microscope for starch and plant or animal tissue. Very frequently several different crystalline compounds can be found, thus giving some idea of the number of ingredients present. Tests of solubility in the more common solvents should be made.

* The best method for volatile oil, however, is that given in a paper by E. K. Nelson, appearing in this issue.

Coating.—The coating from pills and tablets should be removed when possible. This can usually be done by soaking in water and then scraping carefully with a knife. The average weight before and after removing the coating should be determined. Qualitative tests should be made for all probable ingredients of the coating. The usual coating is made of starch, sugar or calcium carbonate and sometimes all three. It is frequently colored and flavored. Special coatings are employed in certain cases, as for enteric pills or tablets, which are coated with salol, a fat, stearic acid, or other material which will not dissolve before reaching the intestines.

Non-Volatile Material.—In determining the non-volatile material as in all determinations of pills and tablets it is best to remove the coating and then powder before proceeding. As a general rule there is very little volatile material present, except moisture or water of crystallization. When water of crystallization is present the drying should be conducted at a temperature sufficiently low to avoid loss of this water or at such temperature that it will be completely driven off. In the latter case care must be taken that the temperature is not great enough to injure other ingredients. The conditions should be recorded.

Ash.—The method is the same as that given under Liquid Preparations.

Sugars.—A great many pills and tablets are sugar-coated and if sugar is found in the coating it should be so noted. In powders and tablets, especially uncoated tablets, lactose is more often used than sucrose.

Chloroform Extract from Acid Solution.—In a large number of cases it is not necessary to use a solution of the material or to make acid; it is sufficient to extract directly with chloroform. If an alkaloid is present with other material it is well to convert the alkaloid to a salt by the addition of acid before extracting the other material with the chloroform. The references have already been given under Liquid Preparations.

Chloroform Extract from Alkaline Solution.—For alkaloids it is best to first dissolve out soluble substances from the sample in about 0.05 *N* sulphuric acid, and then make the solution alkaline and extract with chloroform as directed under Liquid Preparations.

Emodin.—The powdered material may be moistened with hydrochloric acid and emodin extracted directly. (*Loc. cit.*)

Gums, Resins and Inorganic Material.—Tests for these substances are made by the methods used for Liquid Preparations. It must be borne in mind that some of the materials used as excipients, adhesives, disintegrators, absorbents, lubricants and fillers may be found here.[14]

The outline given above is suggested as a general procedure and must be modified more or less in specific instances. Moreover, each product must be studied in the light of all the knowledge which can be obtained as to its probable composition, and in many cases special methods or combinations of methods will be found necessary.

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DETERMINATION OF ALCOHOL AND WATER IN OFFICIAL ETHER.

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A timely article by R. L. Perkins appeared in the May issue of the *Journal of Industrial and Engineering Chemistry* on the determination by specific gravity of the percent by volume of alcohol and water in official ether. The specific gravity (apparent) of the ether at $\frac{25^\circ}{25^\circ}$ is taken, also that of the same ether after dehydration by potassium carbonate. From these data, by aid of charts plotted from data obtained through accurate determinations of the specific gravity of a sufficient number of mixtures of ether, alcohol and water in known proportions, the percentages of alcohol and of water in any given sample are readily deduced.

Examination of the plotted "curves" shows that these for practical purposes may be considered to be straight lines so that, within the narrow range covered by the charts, a certain difference in specific gravity corresponds with a practically uniform difference in percentage of water or of alcohol, as the case may be—the two factors naturally being quite distinct. It is therefore possible to deduce simple formulas by which the proportions respectively of alcohol and of water in a given sample of ether may be deduced from the observed specific gravities of the sample before and after dehydration.

I have not gone into the question of the standard temperature assumed for the measurement of the respective fluids—a matter of some importance since these differ greatly in their coefficients of expansion. Neither have I considered the question of condensation of volume in the mixing of the fluids, which, of course, has its effect on the volume percentage of the several fluids. I have simply used the data as offered in Mr. Perkins' paper and embodied in his charts. From these I have deduced the following mathematical formulas which will give percentages sufficiently exact for all practical purposes.