CHAPTER 2

Gravimetric Analysis

Ronald T. Coutts
UNIVERSITY OF SASKATCHEWAN
SASKATOON, SASKATCHEWAN

2.1 INTRODUCTION

Despite the fact that the processes involved are usually slow and tedious, many substances are most conveniently assayed by gravimetric methods. Such methods of analysis conclude with the weighing of a residue that is obtained from the substance or preparation being assayed by one of a variety of methods (described later). By determining the weight of the residue, the proportion of pure substance in a sample of known weight or volume can be readliy calculated.

It is undoubtedly true that the modern trend in analysis is to employ more rapid and at least equally accurate methods of assaying, such as titrations in nonaqueous media and spectrophotometric determinations. The BP and USP follow this trend; many gravimetric assay processes are being replaced by more convenient procedures. This trend, however, is not always in the one direction. The BP 1948 described a volumetric assay process for zinc oxide ointment. Similarly, the assay of silver nitrate was a volumetric one in the BP 1953. In the current BP, gravimetric methods of assay are described in both monographs. In spite of the trend mentioned above, gravimetric assay methods still remain the choice for many official substances (Tables 2.1–2.4), including some of the more recently introduced medicinals. Of the new monographs in the BP 1963, not included in the original 1958 publication, no fewer than 18 describe a gravimetric method of analysis.

The official gravimetric assays of the BP 1963 and the USP XVII can be conveniently classified into three main groups.

1. Assay processes involving ignition (Table 2.1). Sometimes the sample is directly ignited with or without some form of prior treatment, or else the ignition follows a preliminary precipitation. In both instances, the residue obtained after ignition is weighed.

2. Assay processes involving solvent extraction (Table 2.2). Assays contained in this group can be conveniently subdivided into four types. In some instances extraction yields a product unaltered from the form in which it is present in the substance or preparation being assayed. The majority of examples of this group, however, involve solvent extraction after preliminary treatment with acid or alkali to liberate acidic or basic material, respectively, which can then be extracted into an appropriate organic solvent. Removal of the solvent yields a residue, the weight of which is determined.

3. Assay processes involving precipitation followed by weighing of the precipitate (Table 2.3). Once again, as the table shows, it is possible to subdivide the examples falling into this group. The major process involved in this case is the method whereby a simple chemical derivative of the substance or component of the preparation is made, filtered off, dried, and weighed.

In addition to the three procedures mentioned above, other methods of minor importance are encountered in gravimetric analysis. The official BP and USP examples are listed in Table 2.4.

TABLE 2.1: Gravimetric Assays of the BP and USP Involving Ignition*

Type 1. Direct ignition
- Final residue of Bi_2O_3:
  - Bismuth subcarbonate USP
  - Bismuth subsalicylate USP and sterile suspension USP
- Final residue of SiO_2:
  - Magnesium trisilicate BP, USP and tablets USP (for SiO_2)
- Final residue of ZnO:
  - Zinc cream BP
  - Zinc oxide ointment BP, USP XVI
  - Zinc oxide paste USP XVI
  - Compound zinc paste BP
  - Zinc and castor oil ointment BP
  - Zinc and salicylic acid paste BP

Type 2. Ignition after preliminary precipitation
- Final residue of Au:
  - Sodium aurothiomalate BP and injection BP (for Au)
- Final residue of Al_2O_3:
  - Aluminum acetate solution USP XVI
  - Aluminum chloride USP XVI
  - Aluminum hydroxide gel USP XVI
  - Aluminum hydroxide gel dried USP XVI and tablets USP XVI
  - Aluminum paste USP XVI
  - Aluminum monostearate USP
  - Aluminum subacetate solution USP XVI
  - Aluminum sulfate USP XVI
- Final residue of $BaSO_4$:
  - Busulphan tablets BP
  - Compound calcium cyclamate solution USP XVI and tablets USP XVI (for calcium cyclamate)
  - Ichthammol BP
  - Sodium sulphate BP
  - Sulfobromophthalein sodium BP, USP XVI
  - Sulfur ointment USP
  - Precipitated sulfur USP
- Final residue of $Bi_2(PO_4)_2$:
  - Bismuth subsalicylate sterile suspension USP XVI
  - Emetine and bismuth iodide BP
- Final residue of $Mg_2P_2O_7$:
  - Absorbable dusting powder USP XVI (for MgO)
  - Magnesium sulfate USP XVI
  - Raspberry juice USP
- Final residue of Na_2SO_4:
  - Sodium aurothiomalate BP and injection BP (for Na)
- Final residue of ZnO:
  - Zinc sulfate USP XVI

* All assays designated USP XVI have been either altered in or deleted from USP XVII.

TABLE 2.2: Gravimetric Assays of the BP and USP Involving Solvent Extraction*

Type 1. Extractions yielding a final product in the form in which it is present in the substance or preparation being assayed

Amylobarbitone (amobarbital) tablets BP, USP
Butobarbitone tablets BP
Caffeine and sodium benzoate USP and injection USP (for caffeine)
Carbromal tablets BP
Compound codeine tablets BP (for phenacetin)
Compound codeine tablets, soluble BP (for phenacetin)
Colchicine tablets USP
Desoxycorticosterone acetate tablets USP XVI
Estrone injection USP XVI
Ethisterone tablets BP, USP XVI
Mephobarbital tablets USP XVI
Methoin tablets BP
Methylthiouracil tablets USP XVI
Phenacetin tablets USP
Phenobarbital elixir USP XVI
Phenobarbitone (phenobarbital) tablets BP, USP XVI
Phenolphthalein tablets BP
Picrotoxin injection BP
Progesterone tablets USP XVI
Secobarbital elixir USP

Type 2. Extractions which yield an acid, originally present as a salt or other derivative in the substance or preparation being assayed

Amylobarbitone (amobarbital) sodium BP, USP and capsules BP, USP
Amylobarbitone injection BP and tablets BP
Barbitone sodium BP and tablets BP
Diphenylhydantoin sodium USP and capsules USP
Fluorescein sodium BP, USP and ophthalmic solution USP
Pentobarbitone (pentobarbital) sodium BP, USP and capsules BP, USP and elixir USP and injection USP and tablets BP
Phenobarbitone (phenobarbital) sodium BP, USP and injection BP, USP and tablets BP
Phenytoin sodium BP and tablets BP
Quinalbarbitone (secobarbital) sodium BP, USP and capsules USP and tablets BP
Soft soap BP
Thiamylal sodium for injection USP XVI
Thiopentone sodium BP and injection BP

Type 3. Extractions which yield a base, originally present as a salt in the substance or preparation being assayed

Amodiaquine tablets BP
Chloroquine phosphate USP XVI and tablets USP XVI
Hydroxychloroquine sulphate BP, USP XVI and tablets BP
Papaverine hydrochloride injection USP XVI and tablets USP XVI
Quinidine sulphate BP, USP and tablets BP, USP
Quinine bisulphate BP and tablets BP
Quinine dihydrochloride BP and injection BP
Quinine hydrochloride BP
Quinine sulphate BP and tablets BP
Tetracaine hydrochloride USP

Type 4. Extractions of natural products

Aspidium USP and oleoresin USP (male fern BP and extract BP) (for crude filicin)
Benzoin USP (for alcohol-soluble extractive)
Cacao USP (for nonvolatile ether-soluble extractive)
Colchicum corm BP and liquid extract BP and tincture BP (for alkaloids)
Podophyllum USP (for podophyllum resin)
Storax USP (for cinnamic acid)

* All assays designated USP XVI have been either altered in or deleted from USP XVII.

TABLE 2.3: Gravimetric Assays of the BP and USP Involving Precipitation, Followed by Weighing of Precipitate*

Type 1. Ignition of the precipitate before weighing
See Table 2.1, type 2.

Type 2. Precipitation of a base from its salt
Amodiaquine hydrochloride BP

Type 3. Precipitation of an acid from a solution of its salt
Bishydroxycoumarin USP
Iodipamide methylglucamine injection BP

Type 4. Precipitation of metallic sulfides
Ammoniated mercury ointment USP and ophthalmic ointment USP
Bismuth sodium triglycollamate USP XVI and tablets USP XVI

Type 5. Precipitation of silver or halogen as silver halide
Silver nitrate BP (silver content precipitated as AgCl)
Sodium levothyroxine USP XVI (iodine content precipitated as AgI)

Type 6. Precipitation of a chemical derivative
Aneurine hydrochloride BP and injection BP and tablets BP (silicotungstate)
Betazole hydrochloride USP and injection USP (phosphotungstate)
Dienestrol USP XVI (diacetate)
Hexamethonium tartrate BP and injection BP (reineckate)
Histamine acid phosphate BP and injection BP (nitranilate)
Hydroxyamphetamine hydrobromide ophthalmic solution USP (diacetate)
Iodochlorhydroxyquin ointment USP XVI and tablets USP XVI (copper complex)
Ipecacuanha and opium powder BP and tablets BP (morphine content is precipitated as its 2,4-dinitrophenyl derivative)
Methylene blue USP XVI and injection USP XVI (perchlorate)
Nandrolone phenylpropionate injection BP (semicarbazone)
Penicillin G (benzylpenicillin) BP
Penicillin G (buffered) for injection USP XVI
Potassium penicillin G USP XVI
Procaine penicillin G BP, USP XVI
Sodium penicillin G USP XVI
(Penicillin G content is precipitated as the 1-ethylpiperidinium salt)
Pentolinium injection BP (reineckate)
Phentolamine hydrochloride BP and tablets BP (trichloracetate)
Phentolamine methanesulphonate BP and injection BP (trichloracetate)
Piperazine adipate BP and tablets BP (picrate)
Piperazine citrate BP (picrate)
Piperazine phosphate BP and tablets BP (picrate)
Progesterone injection BP, USP XVI (2,4-dinitrophenylhydrazone)
Proguanil hydrochloride BP and tablets BP (copper complex)
Propyl gallate BP (bismuth salt monohydrate)
Suxamethonium chloride injection BP (reineckate)
Testosterone propionate injection BP, USP (semicarbazone)
Trimethaphan camphorsulfonate USP XVI and injection USP XVI (picrate)
Wool alcohols BP (cholesterol content is precipitated as the digitonide)

* All assays designated USP XVI have been either altered in or deleted from USP XVII.

TABLE 2.4: Gravimetric Assays of the BP and USP Involving Miscellaneous Techniques*

Removal of solvent followed by weighing of the residue
Amaranth solution USP XVI
Collodion USP
Sulfobromophthalein sodium injection USP XVI
Recrystallization from a saturated solution of the pure material
Dicophane BP
Liberation and weighing of the total alcohol content
Sodium lauryl sulfate BP
Weighing of capsules with and without contents
Tetrachloroethylene capsules BP

* All assays designated USP XVI have been either altered in or deleted from USP XVII.

2.2 FACTORS AFFECTING THE VALIDITY OF GRAVIMETRIC ASSAY PROCESSES

A. ASSAYS INVOLVING IGNITION

As Table 2.1 indicates, there are two types of gravimetric assay that involve ignition. The most convenient method is the *direct ignition* of the sample in a crucible to yield finally a nonvolatile inorganic residue (often an oxide of one of the elements present in the sample or preparation). It is obvious that the temperature employed in such a procedure must be high enough to volatilize all except the desired heat-stable product. In some examples of this type of assay process, precautions must be taken to ensure that the final residue is in the desired form and that all other nonvolatile matter is excluded. The USP assay procedures of bismuth subsalicylate and magnesium trisilicate illustrate this. In the former assay, the residue obtained by direct ignition is reignited in the presence of nitric acid. This additional treatment is to ensure that all organic material is oxidized and hence readily volatilized, and also to prevent any reduction of bismuth trioxide to metallic bismuth, which would invalidate the assay process. Magnesium trisilicate is a compound of magnesium oxide and silicon dioxide with varying proportions of water. The SiO_2 content could not be determined by ignition without prior removal of the MgO content, which is also nonvolatile. The BP and USP describe different methods to remove the magnesium oxide, and of the two methods, the one employed by the USP is the simpler. Treatment of magnesium trisilicate with dilute sulfuric acid yields soluble magnesium sulfate and a residue consisting mainly of silica. This residue, after washing, is then ignited.

Another factor that must be borne in mind in ignition assays is that the high temperatures involved can result in fusion of the metallic portion of the residue with the crucible. This, therefore, limits the choice of crucible type. Bismuth salts, for example, must not be ignited in metal crucibles, for metallic bismuth would readily fuse with such crucibles.

Assay processes involving the *preliminary precipitation* of an element of the substance or preparation in a form suitable for ignition are affected by the factors mentioned above, in addition to the factors which affect precipitation techniques, discussed later. It should be noted that, in many examples of this type of assay process, the initial precipitate is not in the form in which it appears after ignition. Table 2.5 illustrates the composition of the initial precipitate in the case of the items listed in Table 2.1 (type 2).

The USP assay process for the citric acid content of raspberry juice is

TABLE 2.5: Composition of Residue Prior to and after Ignition*

Precipitate	Residue after ignition
Au	Au
$Al(OH)_3$	Al_2O_3
$BaSO_4$	$BaSO_4$
$Bi_3(PO_4)_3$	$Bi_3(PO_4)_3$
$MgNH_4PO_4$	$Mg_2P_2O_7$
Basic carbonate of zinc of approximate formula $ZnCO_3 \cdot 2ZnO \cdot 3H_2O$	ZnO
Na_2SO_4	Na_2SO_4

* See also Table 2.1.

novel enough to deserve special mention. On treatment with excess magnesium oxide, the citric acid present forms an equivalent amount of water-soluble magnesium citrate. The surplus magnesium oxide is removed by filtration, and the magnesium in the filtrate (equivalent to the citric acid) is precipitated as magnesium ammonium phosphate, which in turn is ignited and weighed as magnesium pyrophosphate.

B. ASSAYS INVOLVING PRECIPITATION TECHNIQUES

1. Solubility and Physical Form of Precipitate

It is obvious that, for a gravimetric assay of this type to be successful, the precipitate obtained must be so insoluble, under the conditions of the assay, that to all intents and purposes precipitation is quantitative. In addition, the physical form of the precipitate should be such that it is easily filterable. Various factors affect the solubility and the physical characteristics of a precipitate and some of them (solubility product and common ion effect, pH, temperature, time) are mentioned briefly at this point. A detailed discussion of all the pertinent factors is outside the scope of this chapter.

a. Solubility Product and Common-Ion Effect. Where a precipitate is only very slightly soluble in water, it is possible to calculate how much of this

substance remains in solution and how this amount can be reduced to a minimum by having a knowledge of the *solubility product* (SP) of the precipitate. A brief reference to the solubility of silver chloride will illustrate how such a principle influences the method of analyzing the silver or halide content of materials, using gravimetric technique.

Silver chloride is only very slightly soluble in water (0.00179 g/liter at 25°), at which concentration a saturated solution exists. Thus, when a solution of silver nitrate is added to a solution of potassium chloride, the above-mentioned concentration of silver chloride is rapidly exceeded, and a precipitate of silver chloride results, leaving the supernatant liquid still saturated with respect to AgCl. It can be shown that, when the salt is almost insoluble, the product of the molecule concentrations of its ions is constant and is referred to as the solubility product of the difficultly soluble salt.

Thus, $SP_{AgCl} = [Ag^+] \times [Cl^-]$, where $[Ag^+]$ and $[Cl^-]$ are, respectively, the concentrations in moles per liter of silver and chloride ions. A saturated solution of silver chloride in water at 25° contains

$$0.00179 \text{ g AgCl per liter}$$

$$= \frac{0.00179}{143.34} \text{ mole AgCl per liter}$$

$$= 0.0000125$$

$$= 1.25 \times 10^{-5} \text{ mole AgCl per liter}$$

Since the solution is highly diluted, it is valid to assume that the AgCl in the solution is 100% ionized, and therefore a saturated solution of silver chloride will contain

$$1.25 \times 10^{-5} \text{ mole } Ag^+ \text{ ions per liter}$$

$$1.25 \times 10^{-5} \text{ mole } Cl^- \text{ ions per liter}$$

therefore,

$$SP_{AgCl} = [Ag^+][Cl^-]$$

$$= 1.25 \times 10^{-5} \times 1.25 \times 10^{-5}$$

$$= 1.56 \times 10^{-10} \qquad (25°C)$$

Since the product of the molecule concentrations of the silver and chloride ions is constant, it follows that if the concentration of chloride ion is increased by the addition of hydrochloric acid, the concentration of silver ions in the solution will have to decrease to preserve equilibrium, and hence a precipitate of AgCl will result. This is referred to as the *common-ion effect*, which is frequently used in gravimetric analysis to ensure as complete precipitation as possible of products of reaction which are only slightly soluble.

It is important to repeat that the decrease in the solubility of silver chloride caused by the common-ion effect occurs only when dilute solutions of chloride are added. In concentrated chloride solutions, the solubility of silver chloride increases as a result of the formation of complex ions such as $AgCl_2^-$, $AgCl_3^-$, and $AgCl_4^{3-}$, in which the positive silver ion is surrounded by the negative chloride ions.

b. Effect of pH. Generally speaking, there are three main reasons for adjusting the pH of a solution prior to a gravimetric precipitation: (1) to ensure maximum precipitation (This has been discussed to some extent under "common-ion effect."); (2) to prevent precipitation of undesirable compounds; (3) to influence the physical state of the precipitate and to render it more amenable to filtration.

The assay process for sodium sulphate BP illustrates two of these points. The addition of a solution of barium chloride to a solution of sodium sulfate would result in the precipitation of the desired product (barium sulfate), but if carbonate or phosphate impurities were present, barium carbonate and barium phosphate would also precipitate at neutral or slightly alkaline pH. The addition of acid prevents the precipitation of these undesirable products and also prevents the coprecipitation of barium hydroxide. In addition, the presence of acid produces a coarse and therefore easily filterable precipitate of barium sulfate.

c. Temperature Effect. A gelatinous, voluminous, or very fine precipitate is difficult to filter and dry, and is therefore undesirable. Provided the precipitate is stable and sufficiently insoluble, it is often advantageous to perform the precipitation, filtration, and washing of the precipitate at elevated temperature, since precipitates are, generally speaking, more readily coagulated and hence more easily filtered if the solution is hot and dilute. Such a procedure also tends to reduce the possibility of coprecipitation, as substances that could contaminate the precipitate are usually more soluble in hot solution. In addition, solutions are more rapidly filtered when hot, mainly because the viscosity of the solution is lower at elevated temperature.

d. Time Effects. For at least two reasons it is important that a suitable length of time elapses between the addition of the precipitant and the removal of the precipitate. Such a procedure ensures complete precipitation, avoiding the possibility of supersaturation. A time lapse also allows the precipitate to assume a form suitable for easy filtration. Slow addition of the precipitant accompanied by vigorous stirring of the hot solution during addition also induces formation of coarse, easily filterable particles.

2. Purity, Composition, and Stability of the Precipitate

When a precipitate separates from a solution, it invariably carries with it small quantities of the soluble constituents of the solution. This phenomenon

is termed *coprecipitation* and is the result of a variety of causes. Two main causes are *adsorption* and *occlusion*.

Adsorption of material from solution by a solid is a well-known phenomenon. The colloidal suspension of silver chloride formed by adding excess hydrochloric acid to a solution of silver nitrate, for example, is negatively charged, owing to the adsorption of negatively charged chloride ions. Another example, well-known to the chemist, is the use of activated charcoal to remove colored impurities from solution.

Occlusion is a term used to describe the entrainment or mechanical entrapment of portions of solution within crystals or crystal masses.

Since coprecipitated material cannot be removed by washing, certain general procedures should be adopted to minimize this phenomenon. Avoid large excesses of precipitants; use hot, dilute solutions and add the precipitant slowly and with constant stirring to prevent localized high concentrations of reactants. Select a suitable medium for the precipitation, and allow some time to elapse before filtering. Many of these procedures also favor the formation of coarse, readily filtered particles.

Precipitation of barium sulfate is often accompanied by coprecipitation. For this reason, the BP assay process adopts most of the previously mentioned procedures to minimize the coprecipitation.

The final residue which is weighed must be of known composition and be sufficiently stable to be dried at elevated temperatures. This limits the choice of derivative. Hygroscopic residues or thermolabile residues are obviously undesirable, as are residues which tenaciously hang on to solvent and require lengthy periods of heating to render them dry.

C. ASSAYS INVOLVING SOLVENT EXTRACTION

An appreciable number of BP and USP tablets are assayed by extracting a known quantity of powdered tablets with an organic solvent, removing that solvent, and weighing the residue. The solubility of the material desired for weighing and the solubility of undesired substances in the tablet influence the choice of solvent. Generally speaking, acetone, ether, chloroform and, to a lesser extent, alcohol or carbon tetrachloride, are most commonly used though sometimes a mixed solvent is found to be desirable, for example, in the assay of amobarbital tablets USP. Some complications can arise with tablets containing binders or lubricants which would also be extracted by the solvent and would therefore be weighed with the final residue. In these instances, a preliminary extraction with light petroleum (or another solvent in which the desired product is not soluble) is performed, and this initial extract is discarded. Ethisterone Tablets BP or phenolphthalein tablets BP, which are made with a chocolate basis, are two examples of assay processes involving the preliminary extraction of undesirable materials. If stearic acid or stearates are present as lubricants, further modifications in technique are necessary (for example, amobarbital tablets USP).

Complete extraction of the desired product is essential in this type of assay, the limiting factor here being the permeability of the solvent through the powder being extracted. Obviously, it is desirable to powder as finely as possible to present a large surface area to the solvent, but even so, the number of extractions required for complete extraction cannot be readily calculated. The BP and USP either direct that a test for complete extraction be performed (see Section 2.3) or suggest that extraction be continued for such a length of time that complete extraction can be assumed.

In assay processes which involve solvent extractions from aqueous solution using water-immiscible solvents, complete extraction once again must be assured. The main factor affecting this type of assay is the *partition coefficient* of the substance involved.

If a solute is added to two immiscible solvents, it will distribute itself between the solvents in a definite concentration ratio. If C_1 and C_2 are the equilibrium concentrations of the solute in solvents 1 and 2, respectively, Eq. (2.1) results, where the equilibrium constant K is known as the *distribution coefficient* (or *ratio*) or *partition coefficient*. The coefficient has been shown

$$K = \frac{C_1}{C_2} \tag{2.1}$$

to be constant over a range of concentrations of solute, provided relatively dilute solutions are considered. This is "partition coefficient" in its simplest terms. With some solutes, such as organic acids, modifications to the equilibrium expression are required, but a detailed discussion of these modifications is not necesary here.

The best conditions for the complete extraction of a substance from aqueous solution by a water-immiscible solvent can be illustrated by means of an example. Consider the distribution of 0.50 g of a solute between water and chloroform when

$$K = \frac{C_{H_2O}}{C_{CHCl_3}} = \frac{1}{12} \tag{2.2}$$

If the volumes of water and chloroform used are both 100 ml, then

$$K = \frac{0.5 - W}{100} \Big/ \frac{W}{100} = \frac{1}{12} \tag{2.3}$$

where W is the weight in grams of the solute dissolved in the choroform; from Eq. (2.3), $W = 0.46$ g. If, however, four successive extractions, each using 25 ml of chloroform, had been carried out, then after the first extraction

$$K = \frac{0.5 - W}{100} \Big/ \frac{W}{25} = \frac{1}{12} \tag{2.4}$$

from which $W = 0.3750$ g. Similarly, the weights of solute removed by the second, third, and fourth chloroform extractions would be 0.0937, 0.0235, and 0.0058 g respectively, giving a total of 0.4980 g, compared with a total of 0.460 g when one large extraction, using the same total volume of chloroform, was carried out.

This example illustrates that, in assay processes which involve solvent extraction from aqueous solution, the partition coefficient of the solute should favor the water-immiscible organic solvent. More satisfactory extraction results from successive extractions with relatively small volumes of water-immiscible solvent than when a large volume of the same solvent is used.

2.3 TECHNIQUES USED IN GRAVIMETRIC ANALYSIS

In the majority of gravimetric assays that do not involve solvent extraction, there are three distinct operations for which some technical ability is required. These operations are *precipitation, filtration and washing of the precipitate*, and *drying or ignition of the precipitate*. In the gravimetric assays involving *solvent extraction*, a knowledge of additional techniques is required. The general procedures used in these operations are now considered.

A. PRECIPITATION

The precipitation type of gravimetric assay is subject to many sources of error. To minimize these, it is essential that all apparatus used is clean and free of grease; all reagents should be filtered before use, and precautions should be taken to prevent the access of dust from the atmosphere.

Most precipitations are carried out in a clean beaker, equipped with a stirring rod and covered with a watch glass at all times, except during the actual precipitation. For the reasons discussed in Section 2.2B, a slight excess of a dilute solution of the precipitant is added from a burette, with constant stirring, to a hot (but not boiling) dilute solution of the sample. Care should be taken to avoid scratching the surface of the beaker when stirring, as precipitated material adheres to the scratches and is difficult to remove during filtration. The resulting precipitate is allowed to settle, and a few more drops of the precipitant is added. If no more precipitate separates from the supernatant layer, sufficient precipitant has been added. If, however, further precipitation occurs at this stage, the precipitate is again left to settle and the full procedure is repeated using small quantities of precipitant until precipitation is complete. To increase the coarseness of the precipitate and to render it more amenable to filtration, the contents of the beaker are either left for some time or are boiled. Such a procedure is termed "digestion" of the precipitate. Solutions are most often filtered hot. If, however, the precipitate is too soluble in hot water, the contents of the beaker are allowed to cool to room temperature before filtration.

B. FILTRATION AND WASHING

In gravimetric analysis there are two basic methods for removing a precipitated solid for the purpose of drying or igniting it to constant weight. The suspension of the solid may be filtered either through a filter paper or through one of a variety of filter crucibles.

1. Filtration Using Filter Paper

This is the method often employed when the precipitate is to be subsequently ignited in a crucible (usually made of porcelain, platinum, or silica). "Ashless" filter papers are used for this purpose. They are chemically treated filter papers which yield, on ignition, a residue so small (usually less than 0.0001 g for a 9-cm filter paper) that it can be neglected.* The normal filter papers used measure 9 or 11 cm in diameter; a bulky precipitate such as aluminum hydroxide would require a larger paper than a dense precipitate such as barium sulfate. The folded filter paper is placed in a filter funnel of such a size that the top of the filter paper is at least 1 cm below the top of the funnel. The filter paper is moistened with water and firmly pressed against the side of the funnel to exclude all air bubbles. The funnel is then supported over a beaker, usually with the stem touching the side of the beaker (to avoid splashing), and the major portion of the supernatant layer above the precipitate is transferred to the funnel by means of a rubber-tipped glass rod (Fig. 2.1). The liquid in the funnel should always be kept at least 1 cm from the top of the filter paper. The precipitate is then transferred into the funnel in the same way, using a jet of hot water (unless this is undesirable, in which case cold water should be used.) Any material adhering to the beaker can be removed by gently rubbing the beaker with the rubber tip of the stirring rod and can be washed into the funnel as described before. When all the precipitate has been transferred, the stirring rod should be held above the funnel and rinsed with water to ensure that the precipitate has been quantitatively transferred to the funnel. The precipitate should be washed thoroughly at once by carefully directing water onto the filter paper above the precipitate until the precipitate (but not the filter paper) is covered with water. Allow this to drain completely, then repeat the process until small samples of the washings comply with any qualitative tests that the BP or USP may direct. Again allow the filter to drain completely. The precipitate and paper are now ready for drying and ignition.

2. Filtration Using Gooch and Sintered-Glass (or Silica) Crucibles

Gooch or sintered crucibles provide a rapid method of filtering, washing, and drying a precipitate, and their use is preferred to that of filter paper.

* Whasman Papers No. 40, 41, and 42 are examples. They have fast, medium, and slow filtration rates and are used to remove coarse, medium, and fine precipitates, respectively.

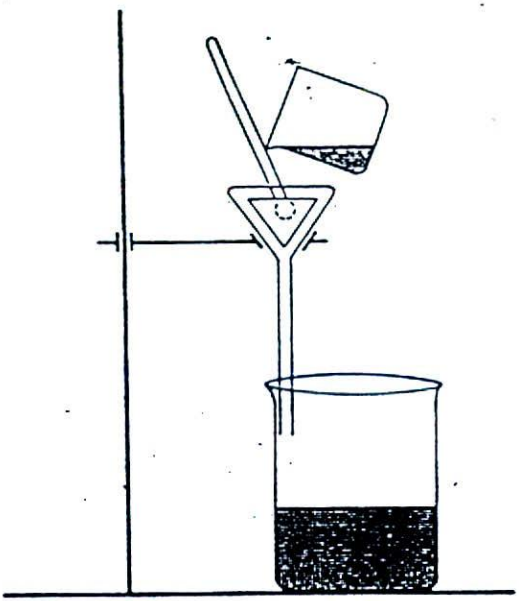


FIGURE 2.1: Filtration using filter paper.

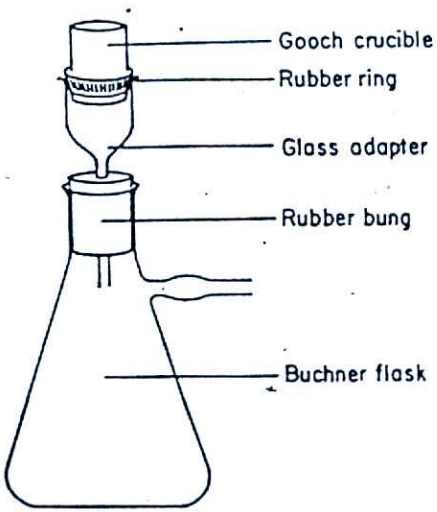


FIGURE 2.2: Filtration assembly using Gooch crucible.

Gooch crucibles or sintered silica crucibles are suitable for the collection of precipitates which require ignition. Sintered-glass crucibles cannot be used for this purpose; they, as well as Gooch crucibles, are used to collect precipitates which are subsequently dried at relatively low temperatures. The trend today is to use filter paper filtration only for gelatinous precipitates (for example, aluminum hydroxide) and crucibles for most other types of precipitates.

a. Preparation of Gooch Crucible for Filtration. A Buchner flask, glass adaptor, Gooch crucible, rubber bung, and rubber ring are assembled as shown in Fig. 2.2. Gooch crucibles have bottoms perforated with small holes; these holes are covered with a thin layer (about 2 mm thick) of asbestos fibers prior to use. This is best accomplished by suspending suitable, commercially available, asbestos fibers in water (about 100 mg in 10 ml) and adding this suspension to the crucible in the assembly (Fig. 2.2). The fibers slowly sink by gravitation, and when most of the fibers have done this and most of the water has passed into the Buchner flask, suction is gently applied to remove the remainder of the water. A uniform pad of asbestos at the bottom of the crucible is the usual result.* To test its suitability for filtration, water is passed through the crucible under reduced pressure; care should be taken not to direct the water onto the asbestos, or the fibers will be dislodged. The filtrate should be free from asbestos fibers and should pass through the crucible at a reasonable rate of flow. The Gooch crucible is then dried or ignited to constant weight under the conditions specified in the BP or USP for the drying or ignition of the precipitate.

b. Drying or Igniting to Constant Weight. The crucible is dried in an oven at a suitable temperature for an arbitrary length of time (say 1 hr), allowed to cool in a desiccator, and then weighed. It is then reheated for 15 min, cooled, and reweighed as before. This reheating process is continued until two consecutive weighings are identical.

The procedure is similar if the crucible has to be ignited to constant weight. The Bunsen or Miker flame is never applied directly to the crucible. Instead, the crucible is placed inside a larger nickel crucible in which it is supported by either an asbestos ring or a layer of porcelain fragments (Fig. 2.3), and the flame applied to the nickel crucible.

c. Preparation of Sintered-Glass Crucibles for Filtration. Sintered-glass crucibles have bases of sintered glass in various porosity grades (Table 2.6). Grade 3 and 4 crucibles are most commonly employed in gravimetric analysis, the former for coarse precipitates and the latter for fine ones. They are

* Sometimes at this stage, steps are taken to prevent the asbestos fibers from dislodging and floating during subsequent filtration procedures, although such precautions are not usually necessary. The fibers can be further compacted by gentle tapping with a glass rod flattened at one end. A perforated plate is also sometimes placed on top of the fibers.

FIGURE 2.3: Crucible assemblies when igniting to constant weight; on left, asbestos ring support; on right, support by means of porcelain fragments.

speedily prepared for filtration by washing under suction with distilled water (or organic solvents) and by drying to constant weight using the procedure previously described for Gooch crucibles. Sintered-glass crucibles have two disadvantages—they must not be heated above 400°C and they are difficult to clean.

d. Filtration and Washing Procedures. The precipitate is transferred to the Gooch or sintered crucible and washed in the manner already described

TABLE 2.6: Sintered-Glass Crucibles

Grade	Pore size, microns
0	150–250
1	90–150
2	40–90
3	15–40
4	5–15
5	1–2

when filter paper is use. A final washing with ethanol to remove most of the water is often beneficial. To avoid dislodging the asbestos pad when Gooch crucibles are employed, suction *must* be applied *before* any liquid is passed through. Samples of the filtrate for qualitative testing can be collected conveniently by inserting test tubes into the Buchner flask.

C. DRYING OR IGNITION OF THE PRECIPITATE

1. When Crucibles are Employed

The crucible and its contents are dried to constant weight by the method previously described for empty Gooch crucibles (see Section 2.3B).

2. When Filter Paper is Used

A silica crucible is preferred to a porcelain one for the ignition process, as the latter type of crucible is more liable to crack and break at high temperature. The crucible (and lid, if it is required) is ignited to constant weight, and in it is placed the folded, well-drained filter paper with its contents. The crucible is then placed in a pipe clay triangle and *gentle* heat is applied by means of a Bunsen flame until the filter paper dries. The heat is then slowly increased to allow the paper to char (but *not* to burn*), and when complete carbonization has occurred, strong heat is applied to volatilize any carbon remaining. The crucible is then heated to the temperature suggested in the BP or USP, the ignition being continued until the weight is constant. Before each weighing, the crucible should be allowed to cool in a desiccator.

D. ASSAYS INVOLVING SOLVENT EXTRACTION

Techniques involved in such assay processes are the same as those discussed in Chapter 8.

1. Test for Complete Extraction

In some BP and USP tablet assays, the powdered tablets are extracted with organic solvents. When a Sohxlet apparatus is used, extraction is allowed to continue for 2 or 3 hr, then the tared flask and the solvent it contains is reserved and replaced with another tared flask containing fresh solvent. Extraction is then allowed to continue for a further ½ to 1 hr. If, after evaporation, the second flask contains no residue, extraction was complete. However, if a residue is present in the second flask, it is redissolved in the solvent, bulked with the contents of the first flask, and extraction is allowed to continue for a further length of time, after which the test for complete extraction is again applied.

In those assays when powdered tablets are stirred or shaken with successive portions of organic solvent and in those assays which involve solvent extraction from aqueous solutions using successive portions of water-immiscible solvents, an arbitrarily chosen number of extractions are carried out and all are bulked. One more extraction is then performed and evaporated separately. If no residue results, the previously bulked solutions contain *all* the extractable material.

2. Removal of Solvent and Drying to Constant Weight

Although the BP and USP do not specify it, a tared "alkaloidal flask" is best for this purpose. Most of the solvent is removed in the conventional manner, using a water bath and condenser. Prior to drying to constant

* Otherwise fine particles would be mechanically lost.

FIGURE 2.4: Removal of residual solvent.

weight, any residual solvent can be speedily removed by rotating the flask on a water bath in order to present a large surface area (Fig. 2.4).

The residue is dried to constant weight in an oven at the specified temperature, using the procedure described in Section 2.3B.

2.4 PRACTICAL GRAVIMETRIC ANALYSIS

Selected examples of compounds and preparations assayed by gravimetric methods are now described. An effort has been made to include mainly assays of organic compounds at the expense of the traditional, but now less important, inorganic examples. Typical calculation procedures are given (lead acetate and methoin tablets).

A. LEAD ACETATE

The BP 1958 describes a gravimetric assay for this compound. The BP 1963 has replaced the 1958 method with a volumetric one using sodium edetate. Nevertheless, the BP 1958 assay process is reproduced here because of its simplicity.

1. Determination of the Percentage w/w $(CH_3COO)_2Pb{\cdot}3H_2O$ in a Sample of Lead Acetate

Theory. The BP 1958 method is based on the reaction:

$$(CH_3COO)_2Pb{\cdot}3H_2O + K_2CrO_4 \rightarrow PbCrO_4\downarrow + 2CH_3COOK + 3H_2O$$

$$379.34 \text{ g } (CH_3COO)_2Pb{\cdot}3H_2O \equiv 323.22 \text{ g } PbCrO_4$$

$$\text{each gram of residue} \equiv \frac{379.34}{323.22} \text{ g}$$

$$= 1.174 \text{ g } (CH_3COO)_2Pb{\cdot}3H_2O$$

Method. Accurately weigh the sample (about 0.3 g), and transfer it to a 250-ml beaker containing a mixture of approximately 100 ml of water and 5 ml of acetic acid (33% w/w). Cover the beaker with a watch glass. Gently boil (Note 1) the resulting solution and to it slowly add with stirring 5 ml (that is, an excess) of an aqueous solution of potassium chromate (Note 2). Boil gently for 15 min (Note 1), remove the source of heat, and allow the

precipitate to settle. The supernatant liquid should be colored yellow, indicating that an excess of potassium chromate has been added. If there is no yellow color, add more potassium chromate solution. Filter through a tared sintered-glass crucible (grade 3) or a Gooch crucible, with the aid of hot water and a rubber-tipped stirring rod, wash with warm water until the washings are colorless, and dry the crucible and contents to constant weight at 120°.

Notes: 1. The BP 1958 suggests heating on a water bath at about 85°. *Gentle* boiling using a Bunsen flame is just as efficient, but care must be taken to avoid too vigorous boiling.

2. Potassium chromate solution BP is an aqueous solution containing 5% w/v K_2CrO_4.

Calculation

	Assay	
	1	2
Weight of sample of lead acetate	0.3018 g	0.2982 g
Weight of residue obtained by BP 1958 assay procedure	0.2557 g	0.2532 g

1st Assay

Each gram of residue is equivalent to 1.174 g $(CH_3COO)_2Pb{\cdot}3H_2O$ in the sample.

$$0.2557 \text{ g residue} \equiv (0.2557 \times 1.174) \text{ g}$$
$$= 0.3002 \text{ g } (CH_3COO)_2Pb{\cdot}3H_2O$$

But this was contained in 0.3018 g of sample.

$$\%\ \text{w/w } (CH_3COO)_2Pb{\cdot}3H_2O \text{ in the sample} = \frac{0.3002}{0.3018} \times 100 = 99.47\%$$

2nd Assay

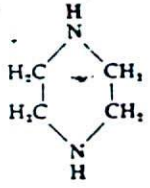
Similarly, % w/w $(CH_3COO)_2Pb{\cdot}3H_2O$ in the sample is 99.70%

These two results are close enough to average.

Conclusion

The percentage w/w $(CH_3COO)_2Pb{\cdot}3H_2O$ in the sample of lead acetate was 99.58%.

B. PIPERAZINE



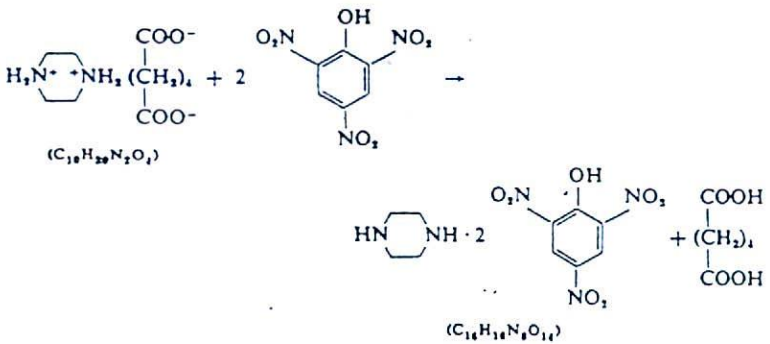
Piperazine, an anthelmintic, is official in the BP 1963 and USP XVII as the citrate. The BP also includes monographs on the adipate and phosphate.

Whereas the USP describes a volumetric assay for piperazine and its preparations (syrup and tablets), a gravimetric assay process is favored by the BP for piperazine citrate, adipate, and phosphate and their preparations. The BP assay process involves the simple precipitation of piperazine dipicrate, the weight of which is determined.

1. Determination of the Percentage w/w $C_4H_{10}N_2 \cdot C_6H_{10}O_4$ in a Sample of Piperazine Adipate

The sample should be previously dried to constant weight at 105°.

Theory. The BP assay process is based on the reaction:



$$232.3 \text{ g } C_{10}H_{20}N_2O_4 \equiv 544.4 \text{ g } C_{16}H_{16}N_8O_{14}$$

$$\text{Each gram residue} \equiv \frac{232.3}{544.4} = 0.4268 \text{ g } C_4H_{10}N_2 \cdot C_6H_{10}O_4$$

Method. Accurately weigh the sample (about 0.2 g) and dissolve it in a solution of 1 N sulfuric acid (3.5 ml) in water (10 ml). Add trinitrophenol solution (100 ml) (Note 1), heat on a water bath for 15 min, then allow to stand for 1 hr (Note 2). Filter through a prepared Gooch crucible or a sintered-glass crucible (Grade 3), previously dried to constant weight at 105°, then wash the residue with piperazine dipicrate solution (Notes 3 and 4) until the washings are free from sulfate. Dry the residue to constant weight at 105°.

Notes: 1. Trinitrophenol solution BP is a saturated solution of picric acid in water to each liter of which has been added 5 ml of a 20% w/v solution of sodium hydroxide in water.

2. This time allows for complete precipitation of piperazine dipicrate in a form suitable for easy filtration.

3. Piperazine dipicrate solution BP is a saturated solution of piperazine dipicrate in water.

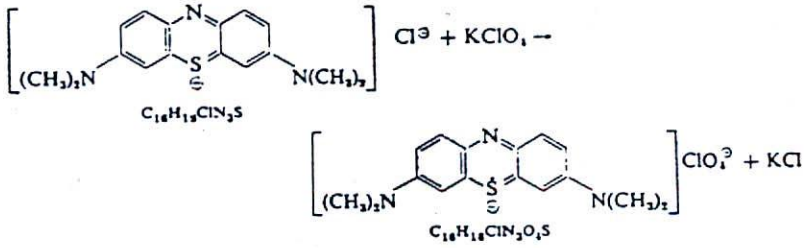
4. The residue must not be washed with water, in which piperazine dipicrate is slightly soluble.

C. METHYLENE BLUE (METHYLTHIONINE CHLORIDE)

1. Determination of the Percentage w/w $C_{16}H_{18}ClN_3S$ in a Sample of Methylene Blue

The sample will have been previously dried to constant weight at 105°C.

Theory. The USP XVI assay process is based on the reaction:



$$319.87 \text{ g } C_{16}H_{18}ClN_3S \equiv 383.87 \text{ g } C_{16}H_{18}ClN_3O_4S$$

$$\text{Each gram residue} \equiv \frac{319.87}{383.87} \text{ g} \equiv 0.8333 \text{ g } C_{16}H_{18}ClN_3S$$

Method. Accurately weigh the sample (about 0.1 g), transfer it to a 250-ml beaker, and dissolve it, with stirring, in approximately 70 ml of warm (70°) water. Allow the solution to cool to room temperature, add approximately 30 ml of a saturated aqueous solution of potassium perchlorate (Note 1), and stir the mixture intermittently for 10 min. Filter, with the aid of 50 ml of methylthionine perchlorate test solution (Notes 2 and 3), through a prepared Gooch crucible (Note 4) previously dried to constant weight at 105°. Finally, wash the precipitate with a further 50 ml of methylthionine perchlorate test solution, then dry the crucible and contents at 105° for 1 hr. Cool and weigh.

Notes: 1. A saturated solution of potassium perchlorate contains approximately 1.54 g of $KClO_4$ in 100 ml of water at 20°.

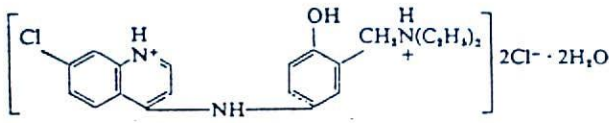
2. Methylthionine perchlorate test solution is a saturated solution of methylthionine perchlorate in water containing potassium perchlorate.
3. Methylthionine perchlorate is slightly soluble in water. The precipitate is therefore washed with methylthionine perchlorate test solution.
4. A sintered-glass crucible (grade 3) is equally suitable.

Additional Notes: 1. The BP assay process for methylene blue uses 0.1*N* titanous chloride. Since such a method determines the total reducing substances, a gravimetric method is more satisfactory.

2. Methylene blue can also be assayed gravimetrically as the picrate[1,2] and the dichromate[3].

D. AMODIAQUINE HYDROCHLORIDE

The USP XVI employs a spectrophotometric method to assay this substance. The BP on the other hand, describes a simple gravimetric procedure. The



$C_{20}H_{22}ClN_3O{\cdot}2HCl{\cdot}2H_2O$ (mw = 464.84)

addition of ammonia to an aqueous solution of the salt precipitates amodiaquine base, the weight of which is determined.

1. Determination of the Percentage w/w $C_{20}H_{22}ClN_3O{\cdot}2HCl$ in a Sample of Amodiaquine Hydrochloride

The sample has been previously dried over phosphorus pentoxide for 24 hr at a pressure not exceeding 5 mm Hg.

Theory. The BP assay process is based on the following reaction:

$$C_{20}H_{22}ClN_3O{\cdot}2HCl + 2NH_3 \rightarrow C_{20}H_{22}ClN_3O\downarrow + 2NH_4Cl$$

$$428.81 \text{ g } C_{20}H_{22}ClN_3O{\cdot}2HCl \equiv 355.87 \text{ g } C_{20}H_{22}ClN_3O$$

$$\text{Each gram residue} \equiv \frac{428.81}{355.87} \text{ g} = 1.2050 \text{ g } C_{20}H_{22}ClN_3O{\cdot}2HCl$$

Method. Accurately weigh the sample (about 0.3 g) and transfer it to a 100-ml beaker. Add approximately 50 ml of water, and stir with a stirring rod until the salt dissolves, than add (with constant stirring) ammonia solution (Note 1) until the solution is alkaline. Allow to stand for 30 min (Note 2), then filter with the aid of water through a prepared Gooch crucible or a grade 4 sintered-glass crucible, previously dried to constant weight at 105°. Wash the precipitate with water until the washings no longer give a reaction for chloride (Note 3); then dry the crucible and contents to constant weight at 105°.

Notes: 1. Dilute ammonia solution BP is a 10% w/w solution of NH_3 in water.
2. This allows for complete precipitation in a form suitable for easy filtration.
3. Test successive portions of the filtrate with silver nitrate solution.

E. ZINC OXIDE OINTMENT

Zinc oxide ointment USP and zinc ointment BP are similar preparations each containing approximately 20% w/w ZnO in suitable bases. Methods of assay employed in the BP and USP XVI are the same.

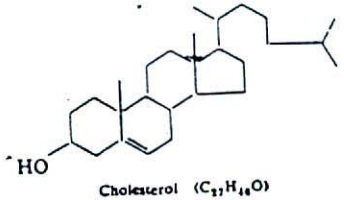
1. Determination of the Percentage w/w ZnO in a Sample of Zinc Oxide Ointment USP XVI

Method. Accurately weigh the sample (about 2 g) in a tared porcelain crucible, and heat with a small flame until the basis is thoroughly charred, then increase the heat until all the carbon is removed and the residue is uniformly yellow. Cool and weigh. Reignite for a further 10 min, cool, and reweigh, and continue this process until the weight of the residue is constant.

Note: This is one of the few examples of a gravimetric process replacing a volumetric method of assay. The volumetric assay process of the BP 1948 is reported[4] as giving equally accurate results, but the gravimetric method is more straightforward and is now preferred.

F. WOOL ALCOHOLS

Wool alcohols BP contain the sterols, cholesterol and lanosterol, together with a mixture of aliphatic alcohols and other minor products. A group of sterols, namely, the 3-β-hydroxysterols, quantitatively form insoluble crystalline addition complexes, termed digitonides, with the steroidal saponin digitonin. Cholesterol is a 3-β-hydroxysterol, and so wool alcohols are conveniently assayed for their cholesterol content.



Cholesterol ($C_{27}H_{46}O$)

1. Determination of the Percentage w/w Cholesterol in a Sample of Wool Alcohols BP

Theory. The BP assay process is based on the following reaction:

$$\underset{\text{cholesterol}}{C_{27}H_{44}O} + \underset{\text{digitonin}}{C_{56}H_{92}O_{28}} \rightarrow \underset{\substack{\text{digitonide}\\(\text{molecular}\\\text{complex})}}{C_{83}H_{136}O_{28}}\downarrow$$

1615.94 g complex ≡ 386.64 g cholesterol

Each gram residue ≡ 0.2393 g cholesterol

Method (Note 1). Accurately weigh the sample (about 1 g) (Note 2), dissolve it in approximately 25 ml of warm alcohol (90% v/v), and filter through a sintered-glass filter (grade 2) while the solution is still warm (Note 3). Wash the residue with 50 ml of warm alcohol (90% v/v), then combine the washings and filtrate in a 100-ml volumetric flask. Cool to room temperature dilute with alcohol (90% v/v) to the 100 ml graduation, and mix. To an accurately measured 10-ml portion of this solution, add 40 ml of a 0.5% w/v solution of digitonin in alcohol (90% v/v), warm to 60°, and allow to stand for 18 hr (Note 4). Filter through a tared sintered-glass crucible (grade 2) (Note 5) with the aid of gentle suction, wash the precipitate in succession with 15-ml portions of alcohol (90% v/v), acetone, and hot carbon tetrachloride (Note 6); then dry the crucible and contents to constant weight at 105°.

Notes: 1. The BP 1958 method of assay has been appreciably altered in the BP 1963.

2. The sample must be thoroughly mixed before weighing. To do this, melt about 20 g on a water bath, thoroughly mix, and allow to cool.
3. The residue consists of long-chain fatty alcohols which must be removed lest they precipitate with the digitonide.
4. Heating to this temperature ensures that complex formation is completed. The time factor allows for complete precipitation of the complex.
5. A prepared Gooch crucible is equally efficient.
6. This treatment removes any material which has precipitated with the digitonide.

Additional Note: Assay for total sterols in Sitosterols NF is a cognate determination.

G. SILVER NITRATE

The BP 1953 describes a volumetric assay using ammonium thiocyanate as titrant, as does the present USP. The BP 1963, however, describes a gravimetric procedure.

1. Determination of the Percentage w/w $AgNO_3$ in a Sample of Silver Nitrate

Theory. The BP assay process is based on the following reaction:

$$AgNO_3 + HCl \rightarrow AgCl\downarrow + HNO_3$$

$$169.89 \text{ g } AgNO_3 \equiv 143.34 \text{ g } AgCl$$

$$\text{Each gram residue} \equiv \frac{169.89}{143.34} = 1.1852 \text{ g } AgNO_3$$

Method. Accurately weigh the sample (about 0.5 g), transfer it to a 600-ml beaker and dissolve it in approximately 300 ml of water containing 3 ml of conc nitric acid (Note 1). Protect the solution from light (Note 2), heat to about 70° (Note 3), and add 0.2 *N* hydrochloric acid dropwise until precipitation is complete and the hydrochloric acid is present in slight excess (Note 4). Keep the solution at 70 to 80°, and stir with a rubber-tipped glass rod until the precipitate is completely coagulated. Cover the beaker with a watch glass and leave for a few hours (preferably overnight) (Note 5). Filter through a tared grade 4 sintered glass crucible (Note 6), with the aid of 0.01 *N* hydrochloric acid, and wash the precipitate several times with 0.01 *N* hydrochloric acid (Note 7). Finally, wash the precipitate with two 5-ml portions of water, and dry the crucible and contents to constant weight at 160°.

Notes:

1. The nitric acid is present for two reasons. It prevents precipitation of impurities such as carbonates or oxides, and it also helps to coagulate any colloidal silver chloride formed.
2. This can be done by carrying out the rest of the assay in subdued light. The reason for such a precaution is that silver chloride is sensitive to light, being decomposed to colloidal silver (purplish color) and chlorine. In diffused light, the error from this source is negligible, even when some darkening of the precipitate occurs.
3. At this temperature, the precipitate coagulates and settles quickly, leaving the supernatent layer clear.
4. If precipitation is complete, the addition of a few drops of hydrochloric acid to the supernatent layer should cause no further precipitation.
5. This is to allow any colloidal precipitate to coagulate completely so that filtration is facilitated.
6. A grade 3 sintered-glass or a Gooch crucible are equally efficient.
7. Water should be avoided at this stage, otherwise the silver chloride may become colloidal and pass through the filter.

H. PHENOBARBITAL (PHENOBARBITONE) SODIUM

The BP and USP describe similar assay procedures for this compound. The BP employs ether as the extraction solvent, whereas the USP uses

chloroform. Each solvent possesses advantages and disadvantages. Some advantages of using ether are (1) barbiturate acids are, generally speaking, more soluble in ether than in chloroform; therefore, fewer extractions are required when using the former solvent; (2) ether is more volatile and therefore more readily evaporated.

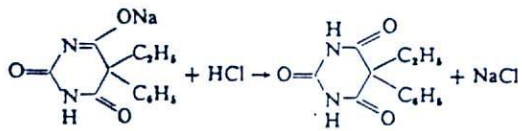
The disadvantages, however, probably outweigh the advantages: (1) Ether is inflammable, chloroform is not. (2) Ether is less dense than water, and therefore the separation technique of extraction assays is more complex than when chloroform is used. When ether is the solvent, three separatory funnels are required for good technique. On the other hand, chloroform is denser than water, and consequently only two separatory funnels are required if it is the extracting solvent. (3) Water is more soluble in ether than in chloroform, a fact which will affect the final drying process.

Chloroform, therefore, is probably preferable, despite the fact that more extractions may be required. The USP assay procedure is therefore described here.

1. Determination of the Percentage w/w $C_{12}H_{11}N_2NaO_3$ in a Sample of Phenobarbital Sodium

The sample has been previously dried to constant weight at 150°C.

Theory. The assay process is based on the fact that, when acid is added to an aqueous solution of phenobarbital sodium, the sodium salt is quantitatively converted into the corresponding acid, phenobarbital, which can be extracted into chloroform leaving any water-soluble impurities in the aqueous layer. By determining the weight of phenobarbital ($C_{12}H_{12}N_2O_3$) so formed, the weight of $C_{12}H_{11}N_2NaO_3$ (pure phenobarbital sodium) present in the sample of phenobarbital sodium can be readily determined.



(I) $C_{12}H_{11}N_2NaO_3$ (II) $C_{12}H_{12}N_2O_3$

$$254.23 \text{ g (I)} \equiv 232.24 \text{ g (II)}$$

$$\text{Each gram residue} \equiv \frac{254.23}{232.24} \text{ g}$$

$$\equiv 1.095 \text{ g } C_{12}H_{11}N_2NaO_3 \text{ in original sample}$$

Method. Accurately weigh the sample (about 0.350 g) and transfer it to a separator containing about 15 ml of water into which the sample will dissolve. To this solution add 2 ml of conc hydrochloric acid and shake well. Completely extract (Note 1) the liberated phenobarbital by successive shakings with 25-ml portions of chloroform.

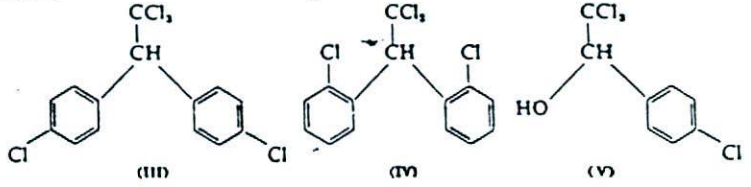
Combine the chloroform extracts and filter through a plug of cotton wool (Notes 2 and 3) into a tared flask (Note 4). Wash the separator and filter funnel with several small portions of chloroform then evaporate the combined filtrate and washings on a steam bath with the aid of a current of air (Note 5). To remove the last traces of solvent add 10 ml of ether, again evaporate, and finally dry the residue at 105° to constant weight (Note 6).

Notes: 1. A test for complete extraction must be performed. As many as eight extractions, each of 25 ml chloroform, may be necessary to extract all the phenobarbital. Initially, extract with four portions of chloroform; then combine and reserve these extracts. The aqueous solution is then extracted with a further 10 ml of chloroform which is evaporated on a tared watch glass. If not more than 0.5 mg of solid residue remains, it is assumed that the combined extract contains all the phenobarbital. If more than 0.5 mg of residue is obtained, further chloroform extractions of the aqueous solution are necessary.

2. This clarifies the chloroform solution and removes traces of moisture.
3. Other filtration methods are permissible.
4. The USP suggests a tared beaker; however, an alkaloidal flask (see before) is preferred.
5. This accelerates the rate of evaporation and also prevents bumping.
6. The normal process of "drying to constant weight" may be applied. However, the USP states that drying at 105° for 2 hr gives, on cooling, a residue of constant weight.

I. DICOPHANE (DDT)

DDT consists chiefly of 1,1,1-trichloro-2,2-di-(4-chlorophenyl)-ethane (III); it also contains some of the isomer 1,1,1-trichloro-2,2-di-(2-chlorophenyl)-ethane (IV), and the carbinol, 1-(4-chlorophenyl)-2,2,2-trichloroethanol (V), as well as other minor products. The sample is assayed for hydrolyzable chlorine and for the 1,1,1-trichloro-2,2-di-(4-chlorophenyl)-ethane content. The latter determination is gravimetric, using a unique method.



(III) (IV) (V)

1. Determination of the Percentage w/w of 1,1,1-trichloro-2,2-di-(4-chlorophenyl)-ethane in a Sample of Dicophane (DDT) BP

The assay is based on the fact that a saturated ethanolic solution of pure 1,1,1-trichloro-2,2-di-(4-chlorophenyl)-ethane at a given temperature (Note 1) will dissolve the other products present in the Dicophane sample but will be unable to dissolve any more 1,1,1-trichloro-2,2-di-(4-chlorophenyl)-ethane at

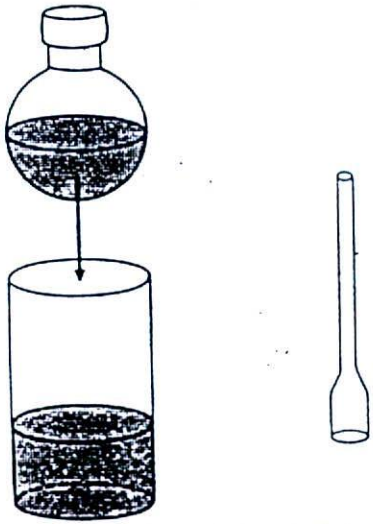


FIGURE 2.5: Apparatus for crystallization, and flat-end stirring rod used in Dicophane assay.

that temperature. Thus, the portion of Dicophane that remains undissolved represents the 1,1,1-trichloro-2,2-di-(4-chlorophenyl)-ethane content of the substance.

Method. Accurately weigh the sample (about 10 g) and transfer it to a 150-ml tall rimless beaker (Note 2). Add 50 ml of 1,1,1-trichloro-2,2-di-(4-chlorophenyl)-ethane solution (Note 3), close the beaker with a flask containing cold water (Note 4) (Fig. 2.5), and heat carefully to dissolve the sample without loss of ethanol. With the flask still in position, allow the solution to cool and, when crystallization occurs, leave for 1 hr, occasionally swirling gently. Leave for a further hour at 17.5 to 18.5° (Note 5); then break the crystalline network with a flat-end stirring rod, and filter with suction through a tared Gooch crucible (Note 6). Wash the beaker with approximately 20 ml of 1,1,1-trichloro-2,2-di-(4-chlorophenyl)-ethane solution, making sure that all the crystals are removed from the beaker, and filter these

washings through the Gooch crucible. Use the flat-end stirring rod to press the crystals down tightly, and allow suction to continue for 5 min. Dry the residue, initially at 40° to remove most of the ethanol, then at 80° to constant weight. The melting point of the 1,1,1-trichloro-2,2-di-(4-chlorophenyl-ethane thus obtained should be not less than 104° (Note 7).

Notes: 1. An ethanolic solution saturated with 1,1,1-trichloro-2,2-di-(4-chlorophenyl)-ethane at 18° is used. When this solution is heated, *all* the Dicophane dissolves, but when the solution is cooled again to 18°, only the 1,1,1-trichloro-2,2-di-(4-chlorophenyl)-ethane content of the Dicophane separates.

2. A beaker of this type makes the removal of the precipitate easier and also facilitates the dissolution of the Dicophane without loss of ethanol.
3. This solution is a saturated solution of 1,1,1-trichloro-2,2-di-(4-chlorophenyl)-ethane in dehydrated ethanol at 17.5 to 18.5°.
4. The flask containing water fits snugly over the mouth of the beaker. It acts as a condenser, which can, of course, be readily removed, and which prevents any loss of ethanol.
5. This ensures complete precipitation. Immerse the beaker in water at 18°.
6. A sintered-glass crucible (grade 3) is equally efficient.
7. Pure 1,1,1-trichloro-2,2-di-(4-chlorophenyl)-ethane melts at 108.5 to 109.5°C. A melting point of the residue lower than 104° would indicate the presence of impurity and would invalidate the assay process.

J. METHOIN TABLETS

The BP assay process for methoin tablets [trade name: Mesantoin, Methetoin (Sandoz)] is based on the simple principle that methoin can be separated from the other tablet ingredients by extraction with chloroform.

1. Determination of the Percentage w/w $C_{12}H_{14}N_2O_2$ in a Tablet of Methoin, of Stated Strength

Method. Weigh and powder 20 tablets. Accurately weigh a quantity of powder equivalent to about 0.3 g of methoin, transfer this powder to a continuous extraction apparatus (Fig. 2.6), and extract with chloroform until complete extraction is effected (Note 1). Remove the chloroform and dry the residue of $C_{12}H_{14}N_2O_2$ to constant weight (Note 2) at 105°. This is the weight of $C_{12}H_{14}N_2O_2$ in the weight of powder taken. By simple calculation (see below) the weight of $C_{12}H_{14}N_2O_2$ in each tablet of average weight is indicated.

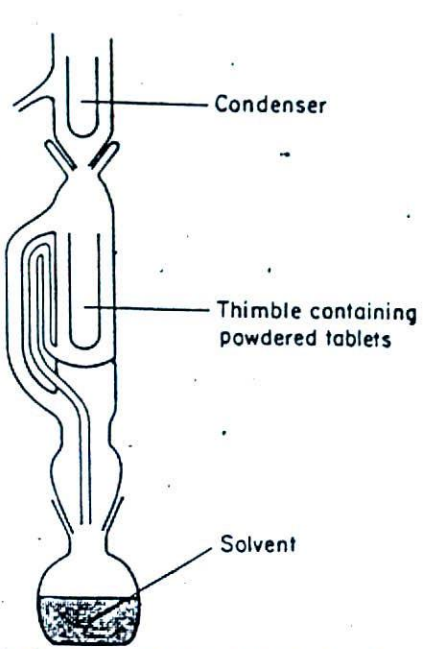


FIGURE 2.6: Continuous extraction apparatus (semidiagrammatic).

Notes: 1. As much as 4 hr continuous refluxing may be necessary. To test for complete extraction, cool, remove, and reserve the flask containing the solvent and replace with another flask containing fresh solvent. Re-extract for a further ½ hr, cool, remove the flask, and evaporate on a steam bath to dryness. The absence of solid residue indicates complete extraction by the initial volume of chloroform.

2. A tared flask should be used.

Calculation

100 mg tablets were used

wt. of 20 tablets = 3.9362 g

therefore wt. of powder approx. equal to 0.3 g methoin $= \frac{3}{20} \times \frac{3.9362}{1}$

$= 0.5904$ g

wt. of powder used in the assay = 0.6028 g

wt. of residue obtained by the *BP* method = 0.3104 g

therefore 0.6028 g powder contains 0.3104 g methoin

20 tablets (3.9362 g powder) contain $\frac{0.3104 \times 3.9362}{0.6028} = 2.027$ g methoin

each tablet contains 0.1014 g methoin

but each tablet is reported to contain 0.100 g methoin

therefore, each tablet contains $\frac{0.1014}{0.1000} \times 100 = 101.4\%$ the stated quantity of methoin

QUESTIONS

Q2.1. List what you consider the advantages and disadvantages of gravimetric methods of analysis. What is the modern trend in analytical procedures? In view of this trend, why is it that some newly introduced monographs in the BP and USP describe gravimetric assays?

Q2.2. A large number of gravimetric assay processes involve the precipitation followed by the weighing of a chemical derivative. What factors influence the choice of a suitable derivative? What precautions must be taken during the precipitation, filtration, washing, and drying of the derivative?

Q2.3. What chemical reactions are involved in the BP and USP XVI assays for the S content of sulfobromophthalein sodium?

Q2.4. The USP and BP describe different gravimetric assays for amobarbital (amylobarbitone) tablets. The BP method is simple, whereas the USP method is relatively complex. What are the advantages and disadvantages of both methods? Explain each step in the USP assay process.

Q2.5. When a sample of lead acetate was assayed according to the BP 1958 method, the percentage w/w of $C_4H_6O_4Pb{\cdot}3H_2O$ in the sample was found to be 103.8%. Explain how such an apparently impossible result, which is within the BP limits, can be obtained.

Q2.6. The BP describes a nonaqueous titration for suxamethonium bromide and its injection and also for suxamethonium chloride, but for suxamethonium chloride injection BP, a gravimetric assay procedure is given. Why is this? Write the equations involved in the gravimetric assay and from it, derive that each gram of suxamethonium reineckate obtained is equivalent to 0.4285 g of $C_{14}H_{30}Cl_2N_2O_4{\cdot}2H_2O$ in the sample.

Q2.7. Dicophane BP is a mixture consisting mainly of 1,1,1-trichloro-2,2-di-(4-chlorophenyl)-ethane. Account for the presence of the isomer 1,1,1-trichloro-2,2-di-(2-chlorophenyl)-ethane and the carbinol, 1-(4-chlorophenyl)-2,2,2-trichloroethanol.

PROBLEMS

P2.1. What is the percentage w/w of $C_{15}H_{11}N_2NaO_2$ in a sample of phenytoin sodium given that 0.4980 g, when treated as describe din the BP assay procedure, produced a residue which weighed 0.4545 g?

P2.2. Use the following information to calculate what percentage of the stated quantity of $C_{21}H_{28}O_2$ is present in a 5 mg tablet of ethisterone.

weight of 20 ethisterone tablets, stated to contain 5 mg of $C_{21}H_{28}O_2$ = 4.8896 g

weight of powder used in the USP assay process = 2.4250 g

weight of residue obtained from the chloroform extraction = 0.05136 g

P2.3. A substance (1.5000 g) is dissolved in water (100 ml). Use the method described in Section 2.2C to calculate how many extractions with 50-ml portions of benzene would be required to ensure that at least 99.5% of the substance had been removed from the aqueous layer, if the partition coefficient,

$$K = \frac{C_{\text{benzene}}}{C_{\text{water}}} = \frac{8}{1}$$

What weight of substance is removed with each benzene extraction? (Assume ideal conditions, that is, that benzene is completely insoluble in water and that complete separation of the two immiscible solvents results after every extraction.) Confirm your answer by using the equation,

$$W_x = \left(W \frac{KV_1}{KV_1 + V_2}\right)^x$$

where W_x = weight of solute remaining in the aqueous layer after x extractions with equal volumes of water-immiscible solvent.

W = original weight of solute in the aqueous layer

K = partition coefficient ($\frac{1}{8}$ in this example)

V_1 = volume of water

V_2 = volume of benzene in each extraction

P2.4. A sample of nitranilic acid, prepared and assayed by the *BP* methods, and found to contain 75.00% w/w $C_6H_2N_2O_3$, was used to prepare nitranilic acid solution BP. If 10 ml of this solution was used in the assay of 0.1525 g of histamine acid phosphate BP, calculate the excess of $C_6H_2N_2O_3$ present, given that the formula of histamine nitranilate is $C_5H_9N_3 \cdot C_6H_2N_2O_8$.

REFERENCES

1. Francois, M. and L. Sequin, *J. Pharm. Chim.*, 10, 5 (1929).
2. Bollinger, A., *Quart. J. Pharm.*, 7, 701 (1934).
3. Ferrey, G. J. W., *Quart. J. Pharm.*, 16, 208 (1943).
4. Garrett, D. C., *The Quantitative Analysis of Drugs*, Whitefriars, London, 1955, p. 522.