ELECTROMETRIC TITRATIONS

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Introduction

The electrometric titrations used in pharmaceutical assays form a special section of the important field of electrometric determinations in chemical analysis, and their development is so closely linked with that of general methods that it is not always easy to separate them. This fact cannot be overlooked when describing recent progress, all the more so because those methods not particularly designed for pharmaceutical preparations may easily be applied to them or, at least, serve as a useful starting point.

The usual reservations must also be made about applying an existing method for assaying a certain substance to all cases. Analytical methods cannot be applied generally; this is even truer in pharmaceutical determinations, where working requirements necessitate the addition to drugs of other substances such as antoxidants, stabilizers, buffers and colouring agents as well as various excipients such as sugar, fats, starch and talc, so that the methods described for the analysis of the pure substance are often of little help to the pharmaceutical analyst, who must solve the problem of detecting, identifying and estimating often extremely small quantities of active substance.

Descriptions of assays taken from pharmaceutical literature and sometimes from general literature will therefore be given.

Except for a few cases, this survey refers to works published since 1951 and, naturally, must not be considered as complete. It does not contain any details of the theoretical principles of electrometric methods, for which the reader is referred to specialized articles. On the other hand, it is well to mention briefly the well-known advantages offered by these methods. First of all, they do not depend on the operator's judgment of the end-point, this always being the most subjective factor affecting the result of an analysis. Secondly, they permit the application of certain methods to highly coloured or turbid solutions, and other cases in which it is not practically possible to use indicators. Furthermore, they can be used in titrating very dilute solutions, with great accuracy, for example graphical methods or simple calculations indicate the end-point much more precisely than the volume of a drop from a burette.

In this way, it is possible to carry out titrations in which as little as 0·03–0·04 ml. of solution are used, with obvious advantages. Finally, the end-point shown by the indicator is not always unaffected by other substances present in the solution for titration, apart from the fact that certain reactions, such as the simultaneous titration of more than one halogen, can be rapidly carried out only electrometrically. The advantages largely compensate for the disadvantages of making numerous burette readings, and also for the necessity for slightly more complicated equipment which may however be adjusted to suit the purpose.

Potentiometric Titrations and Dead Stop

This section summarizes potentiometric methods and the so-called dead stop end-point, which are dealt with together, because they are often applied concurrently.

No description will be given of the basic apparatus usually employed, but it may be stated that this is continuously being improved. The mercury electrode has been suggested as a reference electrode and has been used coupled with the glass electrode. Descriptions have been published of a new mercury-mercurous acetate indicator electrode[1], a modern automatic titrator and a semi-microautomatic apparatus for semi-microanalysis. In order to interpret the results obtained with equipment registering the potential-quantity curves of a solution, apart from the usual methods, the use of the method of concentric arcs has been suggested. A series of concentric arcs is inscribed on a template which is used to determine the centres of curvature of the two parts of the graph on either side of the end-point: the centres are joined by a straight line and the point at which this intersects the graph indicates the end-point.

Much information about the results and methods may be obtained from the literature and reviews, each containing a large number of references. Some of these surveys refer to electrometric methods for pharmaceutical products[3,4] but many more, unfortunately, only to general methods. Particular care has been paid to the discussion and classification of potentiometric methods and equipment for the pharmaceutical analytical laboratory has been catalogued[5]. In order to give an idea of the thoroughness of this survey and its evident interest, *Analytical Chemistry* divided its April 1955 number into two sections, one containing only the surveys and consisting of 116 pages, with almost 3000 references.

Aromatic amines. Up to 5 years ago, only a few attempts[6] had been made to titrate aromatic amines electrometrically using sodium nitrite, and fully satisfactory results had not been obtained. The problem was solved by many investigators between the end of 1950 and the beginning of 1951. We, ourselves, reported[7] excellent results using Pinkhoff's method, the dead stop end-point method, the bimetallic couple method and the normal potentiometric one, and emphasized the advantages of a method that abolishes the use of starch-iodine paper and the consequent indicative tests, and of ice, and, above all, allows the reaction to be carried out even when the liquid is coloured or becomes coloured during the reaction. The method is applicable to many pharmaceutical substances and not only to normal primary amines, but also to other substances of which the NH_2 group reacts with nitrite, for example, sulphonamides, novocaine and *p*-aminobenzoic acid can be titrated by this method.

At almost the same time[8–10], and later[11], other authors, mostly working outside the pharmaceutical field, obtained equally good results, confirming that the method could be used for titrating compounds such as derivatives of aniline, naphthylamine, and amino-anthroquinone, amino-azo dyes and diphenylamine. Each author gives working details of the methods which are rapid, easy[12, 13] and of very wide application.

Aliphatic amines. Aliphatic amines have also been titrated potentiometrically even in mixtures of amines[13].

Halogens. These form one of the groups of ions that most often have to be assayed under widely differing conditions, so that the methods used are very numerous. Some methods have been given of the titration of traces of chlorine[14]. Bromide and thiocyanate in the presence of each other may be determined in acetone at a concentration of 80 to 90 per cent. as the reaction cannot take place in aqueous solutions[15]. Iodides and bromides present in the same solution in the proportion of 1 : 5000 may be titrated argentimetrically, using platinum electrodes in the presence of barium.

Iodides can be titrated with silver nitrate using a hydrogen electrode, and the silver with potassium iodide, both in the presence of *p*-ethoxychrysoidine[16].

Even small quantities of chloride present in solutions of high ionic strength[17], or in organic compounds[18] can be titrated, so that it is possible to combine Pregl's technique with electrometric titration. Some methods now simplify those previously used for chlorine and show that chlorine and bromine can be titrated using amalgamated gold electrodes[19]. Many others are suitable for routine assays[20], for small quantities[21], or for use with automatic apparatus[22]. Even the dead stop end-point method can be used for assaying bromine and iodine present in the same mixture[23].

Free or combined acids. Acids whose salts give an acid reaction on hydrolysis such as aluminium sulphate can be titrated with alkali. Pentavalent phosphoric acids and small quantities of oxalic acid can be titrated using the dead stop method, a potential difference of 200 mV. being applied to the electrodes. Acetic, formic, benzoic, cinnamic, tartaric acids, as well as many alcohols are first oxidized and the excess of oxidizing reagent is then titrated potentiometrically. Under certain conditions, the sulphate ion may be directly titrated with the barium ion. Sodium gentisate may be potentiometrically titrated with iodide solutions, using platinum-calomel electrodes[24].

Alkaloids. Nicotine is titrated[25] with acetic acid and some of its derivatives; morphine and opium[26] by oxidation and very many other alkaloids by precipitation with picrolonic acid[27].

Miscellaneous substances. Vanillin, *p*-hydroxybenzaldehyde, benzaldehyde formaldehyde, furfurol, urea and many other similar products, sulphonamides[28], hydrazine, *iso*nicotinic acid, hydroxylamine[29], hydroquinone, cardiotonic glycosides[30] and tri-(diethylaminoethyloxi-) 1 : 2 : 3-benzene triethiodide[31] have all been satisfactorily titrated.

Dead stop end-point

In view of the wide use of this method, many explanations[32] and clarifications of the principle have been reported[33–35].

Antimony and Arsenic. The dead stop method has been used for the assay, by oxidation with potassium bromate, of important products of pharmaceutical interest, such as the arsenious acid in Fowler's solution

and the antimony in Seignette's salt[36]. Even ascorbic acid has been successfully assayed[36].

Methods in Non-aqueous Media

In recent years, the great possibilities of electrometric methods have been extended to the wide and extremely fruitful field of non-aqueous titrimetry developed from Brønsted's theory; in fact, as has elsewhere been stated, indicators often have only a limited use[37]. Very many basic compounds may be titrated with perchloric acid: sodium derivatives of barbituric acids[38], papaverine[39], alkaline metal salts of aliphatic acids[40], sodium *p*-aminosalicylate[41,42], and caffeine[43, 44]. A good indication of the possibilities of the method is given in a paper[45] reporting the results obtained on 65 different compounds such as alkaline or alkaline earth salts of organic acids, primary, secondary and tertiary amines, amino-acids, amino alcohols, derivatives of pyridine hydrazine and hydrazide, as well as hydrochlorides of various bases the titration of which is made possible by addition of mercuric acetate.

Other investigators[46] have titrated many of these, and other products, such as urea, caffeine, antihistamines[47] present in the form of hydrochlorides, stovaine and lignocaine[48].

Amidopyrine and barbituric acids in the same solution[49], proguanidine[50] isoniazid[51] and certain antihistamines[52], have all been satisfactorily titrated and a general method for antihistamines has been evolved[53]. Titration in non-aqueous media may also be applied to injections in aqueous solution[54], and are especially useful for the active principles of suppositories[55].

Excellent results[56] were obtained for *p*-aminosalicylic, perchloric, formic, phenolic[57] and hydroxybenzoic acids[58]. The possibility of utilizing a wide range of basic solvents permits good differentiation of even extremely weak acids[58]. The effects of the substances being titrated on the slope of the titration curve have been illustrated[59], by over 75 examples; even fatty acids and many of their substitution products can be satisfactorily titrated[60].

Oxidation-reduction titrations can also be performed in non-aqueous media and have been described for various compounds ranging from bromides to permanganate, and hypobromites to sulphonamides[61,62].

Conductimetric Titrations

The application of this method does not seem to be spreading, nevertheless, it is very useful in certain cases: since all the ions present influence the result, the reaction of an ion which produces no potential and without a definite polarographic wave can be studied by conductimetry, and this method often enables ions not taking part in the reaction to be used for qualitative purposes.

Of the latest applications, mention should be made of acid-base titrations in water-organic solvents mixtures[63], the titration of weak organic acids[64] and of weak bases[65] and of hydrochloric and sulphuric acids and their mixtures, in non-aqueous solvents[66]. Barbituric acids (diethyl,

butylethyl, methylphenyl and phenylethyl), their sodium salts and thiopentone, (even mixed with carbonate)[67] as well as amidopyrine[68]—the latter two substances together[49]—and, finally, thiouracil and some derivatives[69], can be titrated conductimetrically.

POLAROGRAPHY

The importance of polarography in metallurgical analysis has long been known. During the last few years, particularly after the Prague Congress (1951), where the wide possibilities of this method were fully emphasized, even organic polarography has been enormously extended.

The increased interest in this field is shown by the work dealing with its theoretical principles and describing increasingly improved apparatus[70] and the new techniques studied for special cases.

A good deal of this development is due, among other things, to studies carried out with anhydrous or mixed solvents which sometimes allow operation in more favourable conditions than those given by aqueous solutions, and also permit the polarographic investigation of numerous organic substances insoluble in water.

The progress of polarographic analysis has widened the horizons but applications to pharmaceutical analysis, although numerous, appear to have only touched the fringe of the subject, if the possibilities of the method are considered.

Metals. First of all, it is necessary to mention the many determinations on metals, these being the most simple ones carried out by the polarographic method, that may be related to, or possibly connected with, some pharmaceutical problems.

Traces of metals have been determined in commercial gelatin[71] biological material, and as heavy metal impurities in organic substances of pharmaceutical interest such as dried yeast, carboxymethylcellulose[72], and in the glass of containers for injections.[73] Polarographic methods have been proposed even for arsenic and are based on the oxidation of the element in alkaline solution, or its reduction in acid[74, 75].

Organic substances containing metals. It is possible to assay polarographically metals present in an organic molecule, e.g., the mercury in phenylmercuric nitrate[76], the cobalt in vitamin B_{12}. This subject has been studied by various investigators, who have reached interesting conclusions on the possibility of distinguishing the various forms of the vitamin[77–80], Renal elimination of cobalt administered as vitamin B_{12} or as the chloride[81], has also been followed.

Vitamins. The polarographic method continues to be successfully used in assaying vitamins. Many studies have been carried out on the various forms of vitamin K, even in non-aqueous solvents, and also on the behaviour of other vitamins: vitamin D_2, analysed in tablet form and in solutions for injection, and whose photolytic decomposition has been followed, with results agreeing with those obtained spectrophotometrically[82]. Vitamin C may be determined in the combined form in vegetable extracts[83] even in the presence of similar substances accompanying it during the vegetative period of the plant, and in the various parts of the

latter. The behaviour of this vitamin in both reduced[84] and oxidized[85] forms has also been reported.

The polarographic behaviour of folic acid has been known for some time, and a method has been put forward for its assay in whale liver oil[86], where its presence has been detected by this same method. The existence of the S-S form along with -SH in aneurine has been demonstrated, and the relative amounts of the two determined[87]. This vitamin has even been assayed in pharmaceutical preparations, within limits of $\pm$ 3 per cent[88].

Research on the behaviour of nicotinic acid and its isomers[89] is still in progress; polarography preceded by separation using ion exchange resins has been used to assay nicotinamide present in extremely small quantities in pharmaceutical preparations and vitaminized powdered milk[90].

Steroids. Further studies have been carried out on the indirect analysis of steroids, using Girard's reagent[91], in order to find a method for their assay in biological fluids. An already known method of determination in aqueous dispersion[92] has been used for directly reducible compounds. The behaviour of some steroids has recently been studied[93], and the polarographic results compared with the colorimetric ones[94].

Alkaloids. Very many analytical methods have been proposed for alkaloids. A direct determination is based on measuring the catalytic current produced by the heterocyclic rings present in the molecule or the diffusion current due to possible reducible groups—as in the case of nicotine[95], the alkaloids of veratrum viride[96,97], and many others. Of all the direct determinations of non-reducible alkaloids, that of scopolamine after nitration[98] and of morphine after treating with nitrous reagents[99], are extremely interesting, as very small quantities can be assayed, the latter even in the various parts of the plant during growth.

Proteins. The characteristic behaviour of the proteins in producing catalytic waves in ammoniacal cobalt solutions continues to be studied, in view of the importance of the assay and properties of proteins in medicine[100]. For example, the catalytic wave method has been used to assay proteins in whey[101]. Furthermore, the possibility of introducing a polarographically reducible group[102, 103] into the molecule has been used for assay, and other indirect methods of analysis have also been applied[104–107]. Substances of high molecule weight, such as proteins, may also be distinguished by the anodic waves they form in suitable base electrolytes[108] and by the reduction or oxidation waves caused by particular functional groups[109, 110].

Antibiotics. The research carried out on penicillin[111] is important, especially for investigating the decomposition processes. New experiments have been carried out on streptomycin, and the tautomerism of its salts has been studied[112]. Analytical methods applicable even to pharmaceutical preparations have been put forward for aureomycin and terramycin[113–115]. Finally, chloramphenicol, which is easily reduced at the electrode because of the presence of the nitro-group, can be assayed polarographically in a series of widely varying pharmaceutical preparations in which it occurs either alone or mixed with various other active

substances; both high and very low concentrations can be determined[116]. Still dealing with analytical control of antibiotic pharmaceutical preparations, mention must be made of the assay of citric acid present in the buffer solution of sodium penicillin products[117], this easily allows the citric acid content of 5 per cent., to be controlled without separation.

Sulphonamides. Sulphonamides may sometimes be determined polarographically, not because of the sulphonamide group, but because of the presence of some other functional group reducible at the electrode, or for their properties as weak acids[118,119], while diaminodiphenylsulphone and its derivatives are easily determined with the polarograph, because the sulphone group is directly reducible[120].

Barbiturates. The special properties of barbituric derivatives leading to the formation of anodic waves have been utilized for the analysis of even extremely low concentrations[121–123]. Thiobarbituric acid derivatives[124], as well of those of thiourea and of 2:3-dimercaptopropanol[125] behave similarly, while the thioketones are reducible at the ketonic grouping[126].

Isoniazid. Isoniazid is another much studied compound of great pharmaceutical interest. It is reduced by the electrode reaction involving four electrons that allow it to be quantitatively assayed, and also permit its degradation by alkaline hydroylsis[127] to be followed.

Iodides and bromides. Indirect methods applicable to the iodate and bromate ions have been described for the halogens and are extremely interesting as they enable traces of these elements contained as impurities in various salts, water and plants to be assayed[128–131].

Sulphur-containing acids. Of all the sulphur compounds, only the sulphites can be directly determined, and it is of interest to report the direct determination of SO_2 in the atmosphere; sulphates may be indirectly determined by a method based on precipitation in the form of lead sulphate and measurement of the diffusion current produced by the excess of ionic lead[132, 133].

Aldehydes. New processes have been worked out for various aldehydes[134, 135], e.g., acrolein in glycerol[136] and chloral hydrate in the presence of chloro- and dichloro-acetaldehyde[137].

Peroxides. Even the study of the various oxidation products has continued to attract attention; the most interesting of these is a study on hydrogen peroxide[138] and another on ether peroxides[139].

Miscellaneous compounds. Some investigators have studied human saliva polarographically for diagnostic purposes[140], and still others, allergenic pollen[141]. Methods for assaying saccharin[142] and salicylic acid[143] have been reported and a method for determining ethylenediaminetetra-acetic acid[144], which is used as a diagnostic agent, in urine; the same compound is also used as a complexing agent[145,146] in other polarographic determinations.

Attempts have been made to solve the problem of assaying *m*-aminophenol in *p*-aminosalicylic acid[147]. As the acetophenone group is easily reducible, ephedrine, acetylsalicylic acid and atropine, which give acetophenone derivatives on acetylation, can be quickly determined by this

method[148]. It is of interest to mention some methods for assaying weak acids which are sometimes linked with questions of a pharmaceutical nature. The indirect oxalic acid method is based on the formation of an acid salt of europium and polarographic determination of the excess metal[149]. The anodic wave produced by gallic acid at a platinum electrode is utilized for assay[150] and a polarographic wave that appears to be caused by kinetic current[151], is employed in the case of boric acid. Even citric acid can be assayed sufficiently accurately, after being transformed into pentabromoacetone[152].

It can be seen that this method has already given great promise in pharmaceutical studies and assays, and promises still further interesting results.

Oscillographic polarography

The polarographic curves given by the oscillograph, represent the current-voltage phenomena for a single drop of mercury, or the potential-time phenomena seen at an electrode when periodic impulses are applied.

Numerous and detailed reports have been published by research-workers specialized in this particular branch of polarography[153–158]; these are mainly useful for the kinetic study of extremely fast reactions occuring at mercury drop, jet or other electrodes[159].

One of these, designed by Heyrovsky, the founder of the method, is of great importance because it deals with oscillographic polarography in pharmacy[160].

All the reactions causing passage of current at the electrode are translated into the characteristic step of the potential-time curve whose graphic representation is known. Apart from the normal curve, by using differential circuits it is possible to obtain curves representing the derivative of the potential in respect to the time, as a function of the time, and these show the electrode reactions more sharply. An oscilloscope of this type has recently been proposed by Heyrovsky for rapid qualitative polarographic analysis, approximately quantitative analysis, control of the purity of organic compounds and the separation of isomers. He also describes a method, carried out with the same apparatus, for determining CS_2, H_2S, HCN and SO_2 in industrial premises[161] and a study on the decomposition of penicillin[162], based on measuring the interval of time elapsing between the first and last steps on the oscillographic curves.

Sometimes the oscillographic method solves problems that cannot be tackled by the classical method, such as the determination of heterocyclic substances of like formulæ for instance when several *iso*nicotinic acid derivatives are contained in the same preparation[163].

Reports have also been published on substances of specific pharmaceutical interest such as vitamin B_1[164], and so have some preliminary communications promising greater development of oscillographic polarography in quantitative analysis, for example the article putting forward the possibility of using the oscillograph as a means of indicating the end-point of a titration[165].

ELECTROMETRIC TITRATIONS

AMPEROMETRIC TITRATIONS

The amperometric method, which is directly related to polarography, may be applied in all cases where constant diffusion current and a given voltage occur; it does not matter whether these are due to the reagent, to the substance under examination, or to both, so that even non-depolarizable compounds may be titrated with a reagent producing a diffusion current. In practice, the variations in current occurring at a rotating metallic electrode to which a suitable constant voltage has been applied, and due to the addition of an appropriate reagent, are carefully followed. In special cases, two equal electrodes are used without a reference one and this case is identical to the dead-stop end-point mentioned earlier.

The possibility of measuring extremely small diffusion currents extends the application of amperometric technique to microanalysis—e.g., chlorine in concentrations as low as 5×10^{-5} normal[166], halogens and other elements in organic substances.

The assay of *p*-aminosalicylic acid with potassium bromate[167] can be carried out using a rotating platinum electrode to which the constant voltage of + 0·2 V. (S.C.E.) is applied.

p-Diazobenzenesulphonic acid, which is polarographically reducible, may be used as the titrating agent for numerous substances such as sulphonamides and alkaloids, present in quantities of only 2 to 50 mg.[168] with an error of $\pm$ 3 per cent. Lead nitrate titration has been used for assaying glycerophosphates in solutions for injection and even for the assay of tartrates, while phenazone and irgapyrine can be titrated by precipitation with mercuric perchlorate, measuring the current due to the excess of reagent at a dropping mercury cathode without applied potential.

The titration of metallic ions in pharmaceutical preparations has been carried out by methods based on the formation of complexes with ferricyanide ions or on precipitation with dodecylmercaptan and titration of the excess of reagent with silver nitrate; this second method has also been used for assaying micrograms of heavy metals in pharmaceutical specialities.

The choice of reagents producing large diffusion currents is of importance for amperometric titrations. Silicotungstic acid has been used for alkaloids (nicotine, nornicotine); sodium hypobromite has been utilized in titrating even traces of ammonia, and the same method can be used for determining organic nitrogen.

The property of ethylenediaminetetra-acetic acid to form anodic waves has been utilized in assaying metals, giving good results for Mn^{++}, Co^{++}, Ni^{++}, Cd^{++}, Hg^{++} and Zn^{++}, and less satisfactory ones for the alkaline earths[169]. In the case of calcium, still using the same reagent, it is advisable to apply a constant voltage of $-1{\cdot}7$ V. to the electrode, the end-point being when the diffusion current of the calcium finally disappears[170].

Finally, the property of forming complexes with mercury, has been utilized in the amperometric assay of barbiturates.

COULOMETRIC METHOD

Of all the electrometric methods, coulometry is the best able to provide results having an absolute value. It does not depend on the individual

judgment of the operator, nor upon the accuracy with which the strength of a reference sample has been determined because the measurement in coulombs replaces the sample of known strength.

The method may be carried out in two ways: 1) the substance reacts at the electrode, and the number of coulombs required for the electrolytic reaction is measured; 2) a substance suitable for reacting with the one to be assayed is produced at the electrode. In this case, the generating electrode may be immersed in the same titration solution, or in another from which the reagent is run into the solution being assayed.

When the current intensity is kept constant, it is sufficient to measure the time for completion of the reaction, calculate the coulombs from the product of time and the current and, hence the exact quantity of the substance under examination that has been electrolysed, or that of the reagent produced reacting with that under assay.

The advantages of the coulometric method are most evident when the whole operation is completely automatic, as when automatic current-recording equipment is used.

This method gives accurate macro determinations, but the chief advantage over other conventional methods lies in its application to micro-assay, either by direct electrolysis[171, 172] or where the reagent is electrolytically prepared. It is possible, by choosing the right intensity of the current, to prepare as little as 10^{-12} and 10^{-17}g. of reagent, as well as to determine the end-point of titrations carried out with such small quantities, by means of precise potentiometric[173] or, better, amperometric measurements[174], using suitable circuits. As little as 0·01μg./ml. of ferrous iron[174] and 0·001–0·0005 μg./ml. of manganese may be assayed in this manner.

Coulometric methods have been proposed for neutralization reactions[175, 176], with external or internal preparation of the reagents[177].

A method for the assay of sodium thiosulphate has been proposed, based on the electolytic preparation of iodine from potassium iodide[178]; the chlorine produced from hydrochloric acid by electrolysis has been used in titrating *iso*nicotinic hydrazide[179] and long chain unsaturated fatty acids. Similarly, salicylic acid[180] and arsenious ions may be assayed by producing the bromine reagent electrolytically.

The possibility of titrating iodide ions with electrolytic silver ions has been reported, the end-point being determined by means of two silver indicator electrodes, as for the dead-stop end-point[181]; another useful method for assaying chlorides, bromides, iodides, and, in general, all those cases requiring silver ions, makes use of a potentiometric circuit for determining the equivalent point, allowing errors of only $\pm$ 0·005 mg. for quantities ranging from 10 to 0·2 mg.[182].

By allowing thiourea to react with solutions of silver bromide and potentiometrically titrating the bromine liberated with silver ions produced electrolytically, it is possible to assay microgram quantities of thiourea, either alone or in mixtures with other sulphurated compounds[183].

The coulometric method has wide possibilities and numerous new procedures are being proposed by investigators. A new indirect method of analysing mixtures of halogens has been discovered, by combining

coulometric measurement with the weighing of deposited mixtures of silver chloride and bromide[184].

Other investigators have proposed following the course of coulometric titrations by photometric measurements carried out in parallel with them. A photoelectric cell for use with the Beckmann spectrophotometer has been designed for this purpose[185]. Automatic photoelectric apparatus for the determination of the end-point has been suggested[186] and even a differential photometric apparatus has been designed, to overcome the formation of air bubbles at the generating electrode[186].

High Frequency Titrations

Electrometric analysis has recently been extended by a new method utilizing changes in the dielectric constant, the magnetic susceptibility and conductivity at high frequency on altering the composition of the medium. For measuring the dielectric constant, the vessels containing the solution for assay are connected to two metallic surfaces, acting as condensers; the magnetic susceptibility is measured by introducing the vessel with the solution into a solenoid.

General, theoretical and critical articles have been published on this subject[188, 189], as well as those describing the various types of instrument in use and the theoretical principles on which they are based. Others examine experimental data on various solutions, as a function of the various factors[194–198].

Although this method is very recent, several applications have already been described: neutralization[191, 198, 199], oxidation[191] and precipitation titrations[200–203] have all been reported.

Dilute solutions of metallic ions have been titrated with oxime solutions[204] and even the most recent forms of titration, using non-aqueous solutions have been successfully carried out using high frequency apparatus[205, 206].

This method, which has already found some applications in medical and pharmaceutical analysis[206], has certain disadvantages since many factors must be kept constant. Nevertheless, present experience has shown its wide range of possible application, particularly in solving special problems.

For reasons of space the paper as presented at the F.I.P. has been abbreviated and the references have been reduced. The authors will be pleased to give the full references to any who write for them.

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