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Recent applications of electrochemical techniques to the analysis of pharmaceuticals*

L. G. CHATTEN

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada T6G 2N8

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The past decade has revealed a remarkable and renewed interest in the application of electrochemical techniques to the analysis of drugs and pharmaceuticals. In addition, several of these techniques are now being employed to elucidate electrode processes by studying the mechanisms involved in organic redox reactions. The renewed interest in electrochemical techniques can be attributed in part to more sophisticated instrumentation and to an increased understanding of the techniques themselves. This paper selectively reviews recent applications of the following electrochemical modes in the analysis of drugs and pharmaceuticals: amperometry, conductometry, coulometry, ion-selective electrodes, potentiometry, stripping voltammetry (anodic and cathodic) and voltammetry.

Amperometry

Although the recent application of this technique to the analysis of drugs and pharmaceuticals appears to have been limited, two or three interesting applications have been reported. One [1] involved the quantitative determination of phenacetin and acetarsol in which about 0.5 g of either substance was carefully heated with 40 ml of 20% H_2SO_4. When the mixture became clear, it was boiled for 8–10 min, cooled and diluted to a known volume with water. An aliquot of the solution was mixed with 10 ml of 20% HCl and 2 g of KBr and then titrated with 0.1 M $NaNO_2$. The endpoint was detected amperometrically with a rotating platinum electrode and a saturated calomel reference electrode.

Another report [2] described the determination of mefenamic acid in dosage forms. The method was based on its oxidation at a rotating (600–1000 rpm) platinum electrode

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maintained at +0.3 to +0.83 V vs the SCE in the presence of 0.1 M NaOH. The height of the wave was proportional to the content of mefenamic acid from 0.25 to 10 mg in 10 ml of solution. Other normal components of suppositories, ointments and tablets did not interfere with the assay.

Hydrodynamic modulation voltammetry (HMV) at a rotating disc electrode (RDE) has been demonstrated to be a very useful technique for trace analysis [3, 4]. Wang and Freiha [5] have made use of the HMRDE system for the titration of 0.74 μM ascorbic acid with iodine. They employed the stopped rotation means of endpoint detection; the electrode was rotated at 1600 rpm for 15 s and then turned off for 30 s. The process was also applied to the analysis of vitamin C in commercial tablets.

Conductometry

This technique has not enjoyed popularity as a research tool, but some applications are noteworthy. Roy and Prakash [6] reported the determination of diloxanide furoate by hydrolysing the pure solution or aqueous extracts of tablets with 0.5 M NaOH on a boiling-water bath for 1 h, then titrating the cooled and filtered solution with 0.1 M HCl. The endpoint was determined conductometrically.

The conductometric analysis of pholcodine has been utilized by Popovic *et al.* [7] who investigated two procedures. In the first a solution of pholcodine (5–15 mg) in anhydrous acetic acid was titrated with 0.05 M acetous perchloric acid. In the second method, an ethanolic solution of pholcodine was titrated with aqueous tungstosilicic acid. Both methods gave accurate and reproducible results, either with the pure substance or commercial capsules. Certain inactive ingredients in the dosage form contributed to the conductance of the solution, but did not affect the determination.

Conductometry was used by Preti *et al.* [8] for the resolution of mixtures of organic acids by their titration in 2-methoxyethanol with 0.1 M *N,N'*-diphenylguanidine as titrant. Although pharmaceuticals were not assayed, many of the acids involved were of pharmaceutical importance. Individual acids in multicomponent mixtures could be determined with clear conductometric endpoints. The pK_a values of the acids were frequently too close to permit resolution in aqueous media.

In another report [9], phenolphthalein was titrated, as an acid, in an aqueous 30% ethanolic medium with standardized NaOH solution. The endpoint was obtained conductometrically and the inflection on the titration curve corresponded to the titration of the two phenolic protons. The method has been used to determine the phenolphthalein content in drug mixtures without interference from substances such as sulphur, fennel oil or the constituents of senna or belladonna leaves.

Ion-selective Electrodes

Although the field of electrochemistry gives the impression of being settled and established, new developments continue to appear. One area currently under intensive investigation is the modification of solid electrodes. This takes the form of either chemical alteration or coating of the electrode surface with a thin layer of a polymer designed to perform a specific function. There have been a few recent reports dealing with the application of this technique to the analysis of drugs and pharmaceuticals.

Cunningham and Freiser [10] prepared coated-wire ion-selective electrodes for

methadone, methylamphetamine, cocaine and protriptyline based on dinonylnaphthalene sulfonic acid (DNNS). The authors reported selectivity coefficients for the four protonated amines and noted that selectivity decreased with decreasing molecular weight. The detection limits ranged from $10^{-6.5}$ M for protriptyline to $10^{-5.5}$ for cocaine and methylamphetamine.

Rizk *et al.* [11] developed a titrimetric method with ion-selective electrodes for the determination of acetylenic hypnotics. The sample containing 100 mg of ethchlorvynol, ethinamate or methylpentynol carbamate was mixed with 50 ml of ethanol, a filtered 10 ml portion was diluted to 100 ml with ethanol, 5–10 ml of ammoniacal 1 mM Ag was added and the mixture diluted to 100 ml with water. The resulting solution was titrated with 0.5 or 1 mM NaI or KI while the endpoint was detected with an I^- selective electrode and a single-junction reference electrode. Recoveries ranged from 95.7% to 110.8% for 0.1–20 mg of the hypnotics.

A further report [12] described atropine analysis in belladonna extract or suppositories with an ion-selective electrode. The atropine was complexed with picric acid and extracted into chloroform from the aqueous phase that was at pH 4.5 (acetate buffer) and was 4.5 mM in picric acid. A portion of the extract was mixed with water (1:2–1:4) and the extracted picric acid (which corresponded to the atropine in the sample) was titrated potentiometrically in the two-phase system with aqueous 0.35 mM crystal violet. A picrate-sensitive electrode based on crystal violet-picrate solution in nitrobenzene was used as the detector. The coefficient of variation was less than 3.3% when determining *ca* 0.22–0.92 mg of atropine in belladonna extract or suppositories.

Potentiometry

Of the electrochemical techniques dealt with in this paper, conventional potentiometric titrations remain the most popular method for the analysis of drugs and pharmaceuticals. Malecki and Starościk [13] presented yet another means of analysing sulfonamides (by using a silver sulphide membrane electrode). Its response was studied for those sulfonamides forming soluble complexes with silver (sulfacetamide, acetazolamide, furosemide and hydrochlorothiazide), and for those precipitating silver ions (e.g. sulfathiazole and sulfadimethoxine). Solutions were maintained at pH 9–12 and some quantitative results were reported with tablets.

Most potentiometric two-phase titrations of organic acids and bases have been performed manually. A recent report [14] demonstrated the practicality of automatic potentiometric two-phase titrations by using ionic surfactants to promote formation of a micellar phase, thus reducing electrode signal noise.

Christopoulis *et al.* [15] carried out potentiometric titrations on quaternary ammonium compounds, cationic surfactants, alkaloids and other pharmaceutically important substances with 0.01 M sodium tetraphenylborate. The working electrode was a liquid membrane with tetrapentylammonium tetraphenylborate dissolved in 4-nitro-*m*-xylene as the liquid ion-exchanger. The reference was a double-junction silver–silver chloride electrode. Near-Nernstian response to the tetraphenylborate anion was observed over the range of 5×10^{-6} to 3×10^{-4} M.

Chloramine-T (CAT) has been employed as a titrant by Verma and Gupta [16] for the determination of a broad spectrum of sulfonamides in pharmaceutical preparations. Potentiometric endpoint detection employed a saturated calomel and platinum electrode pair.

Voltammetry

Anodic stripping

This technique seems not to have been applied to the analysis of drugs and pharmaceuticals (since virtually all medicinal agents are organic substances) but a paper by Andruzzi *et al.* [17] is nonetheless of interest. They utilized a previously developed "long-lasting sessile-drop" mercury electrode in differential pulse anodic-stripping voltammetric analysis of natural waters, and presented data for the subtrace metal analysis of zinc, cadmium and lead in sea-water.

Cathodic stripping

Ethynylestradiol, a synthetic steroid hormone, occurs in pharmaceutical products that are generally referred to as combined low-dosage oral contraceptives. Bond *et al.* [18] developed a method which combined reverse-phase liquid chromatography and cathodic stripping voltammetry. The working electrode was an HMDE while the reference electrode was a Ag/AgCl saturated with NaCl. Data for the analysis of two dosage forms, both of which contained a combination of ethylnylestradiol and laevonorgestrel, showed impressive recoveries. Detection limits for the steroids were about 5×10^{-9} M, within the limits required for biological media.

Differential pulse voltammetry

A carbon paste electrode (CPE) with a renewable surface was developed by Lechien *et al.* [19] to replace the dropping mercury electrode in the range of positive potentials. The CPE consisted of a viscous fluid of suspended carbon particles packed in a pool and placed in a glass or teflon tube. It had a working range of +1.2 V to −1.0 V vs SCE, and its surface could be renewed by wiping with a tissue or filter paper. The system was used at pH 4.7 for the analysis of ascorbic acid in pharmaceutical tablets and in fruit juices, with very reproducible results.

The morphine content of poppy straw concentrate was determined voltammetrically at a glassy carbon electrode [20]. The method was rapid, sample preparation was minimal and the results were in close agreement with those obtained by HPLC and GC methods.

Adriamycin, a member of the anthracycline antibiotics used in the treatment of certain human cancers, was determined electrochemically in urine by preconcentration at carbon paste electrodes [21]. The method was rapid, accurate and required no sample preparation. For each sweep, a fresh carbon paste surface was immersed in an unstirred solution for 3 min, rinsed thoroughly and the differential pulse voltammogram obtained by immersing the electrode in a fresh solution of the buffer-electrolyte. The limit of sensitivity was 10^{-8} M.

Smyth *et al.* [22] observed that copper (II) forms a labile chelate with bromazepam in acetate buffer at pH 4.8. When this complex was subjected to differential pulse voltammetry with a hanging mercury drop electrode, it gave rise to a catalytic phenomenon which could be used for the assay of 10^{-5}–10^{-9} bromazepam.

A recent publication by Ivaska and Nordstrom [23] described the electrochemical determination of some cephalosporins. Of the compounds studied, only cefadroxil gave a distinct anodic wave at the glassy carbon electrode. Although the waves were not well resolved, it was observed that the reproducibility was better in neutral and alkaline solutions. The diffusion controlled current was found for the anodic oxidation of the 7-position aromatic −OH group and this irreversible wave resulted from a 2-electron oxidation at low pH solutions and a 1-electron removal at high pH. The best recoveries

were obtained when a new voltammogram was constructed each time by subtracting the background voltammogram, the maximum current being measured. Concentrations were at the 10^{-4} M level.

Coulometry

Although the use of constant current coulometry with electrically generated titrants was used some years ago for the analysis of drugs and pharmaceuticals, recent applications have been few. In the author's laboratory controlled potential coulometry is used routinely to assist the determination of the number of electrons involved in electrochemical processes. The values obtained, together with isolation of the resulting product from the coulometric cell, permit reaction mechanisms to be postulated. Two recent examples involved studies on zomepirac sodium [24] and minoxidil [25].

Conclusions

This paper has presented an overview of applications of electrochemical techniques to the analysis of drugs and pharmaceuticals. The examples presented suggest that much more use could be made of these versatile techniques.

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