Journal of Pharmaceutical & Biomedical Analysis
Vol. 7, No. 7, pp. 789–812, 1989
Printed in Great Britain

0731–7085/89 $3.00 + 0.00

Review

The use of ion-selective electrodes in the determination of drug substances

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Abstract: The use of ion-selective electrodes and potentiometric techniques in the analysis of drug substances are reviewed. Sensors for potentiometric measurements, potentiometric ion-pair and complex formation-based titrations, titrants, and applications are discussed. Other potentiometric methods used in the analysis of pharmaceuticals are discussed.

Keywords: *Ion-selective electrode potentiometry; potentiometric titration; drug substances determination.*

Introduction

The development of ion-selective electrodes during the last 20 years has quickly been followed by many applications in addition to those in inorganic analysis. The field of applications was broadened by the introduction of liquid ion-exchanger membranes, membranes containing electroneutral macrocyclic compounds, enzyme electrodes and gas sensors. Such new electrode materials facilitated the development of potentiometric sensors for most of the important inorganic ions and several types of organic compounds, many of which are of ionic character.

With regard to the applications of ion-selective electrodes in the analysis of organic substances, there are, in general, some specialized sources dealing with the matter [1–5]. Some of the books or review papers are directly devoted to the analysis of substances of pharmaceutical interest [6–11, 259]. Persons interested in applications of enzyme electrodes and other bioelectrochemical sensors can find useful information in other comprehensive sources [12–15]. Trends and recent applications of ion-selective electrode potentiometry in determinations of the drug substances are summarized in the present paper.

Ion-selective Electrodes

Ion-selective electrodes are electrochemical sensors that allow potentiometric measurements of the activity of particular species in aqueous and mixed solvents, or

partial pressures of dissolved gases in water. These sensors may respond to certain other ions in the sample, in addition to the selected ("*i*") ion; interferences by such "*j*" ions are usually expressed by Nikolskii's equation

$$E = \text{constant} + f\frac{2.303\ R\ T}{z_i\ F}\log\{a_i + \sum_j k_{i,j}^{\text{pot}}\ a_j^{z_i/z_j}\},$$

in which E is the experimentally observed potential of an ion-selective electrode, $k_{i,j}^{\text{pot}}$ is the potentiometric selectivity coefficient, the "constant" term includes the standard potential of the indication electrode, the reference electrode potential and the junction potential, "*f*" is a correction for non-Nernstian response, terms z_i and z_j denote the charge of the ions "*i*" and "*j*". A galvanic half-cell, represented by an ion-selective electrode immersed in the sample solution under test, consists usually of an ion-selective membrane, an internal electrolyte and an internal reference electrode, and has the typical shorthand form, e.g.

Ag	AgCl	internal electrolyte (Q^+, Cl^-)	membrane permselective to Q^+	test solution.

This represents a conventional construction of the sensing element; the other half-cell is represented by an external reference electrode, e.g. a saturated calomel electrode.

Ion-selective electrodes may be classified according to the nature of the basic membrane material. The main requirement is that the membranes are as immiscible as possible with respect to the bathing solutions and solid contacts. Useful membranes are often solid or liquid electrolytes, because they are composed of partially or completely ionized acids, bases, or salts, or because they contain potentially ionized species.

Solid-state membrane electrodes

These include membranes composed of solid salts, which may be single crystals but are more often polycrystalline pellets pressed from powdered starting material. Heterogeneous combinations of precipitates held in a polymer matrix may also be used.

Liquid ion-selective electrodes

These include membranes made of liquid electroactive substances or with electroactive substances dissolved in a suitable water-immiscible solvent, called the mediator. Furthermore, they also include those containing the electroactive substance in polymeric supports with gelling agents (plasticizers). In addition, the electroactive materials used in the membranes are either the ion-exchangers (hydrophobic acids, bases and salts), or the neutral carriers (valinomycin, nonactin and various crown ethers).

Glass membrane electrodes

These are the oldest and best known ion-selective electrodes, made of various multicomponent glasses.

Electrodes with suitable additional membranes

Examples include gas-sensitive electrodes and biocatalytic membrane electrodes, the

potentiometric detection unit of which is based on conventional electrodes of the previous types.

Construction of a Typical Drug Substance-selective Electrode

Although electrodes of all types mentioned above can be applied to analyse pharmaceutical compounds (for example, halide ion-selective solid-state electrodes have often been used in determinations of compounds containing quaternary nitrogen and a counter halide ion), the typical drug substance-selective electrodes are usually those of the liquid membrane type. It should be noted that virtually any ionic species can be detected and measured by liquid ion-exchanger electrodes. The principle for design is as follows [16]: to build a membrane-electrode responsive to ion X^-, for example, the salt Q^+X^- should be incorporated into a non-volatile solvent, and the Q^+ ion must be highly lipophilic. Similarly for an electrode responsive to cation Q^+, an oil-soluble salt Q^+X^- is used, where the X^- ion is lipophilic. Thus, the quaternary long-chain alkyl and aryl ammonium salts and high molecular weight cationic dyes, etc., are known to behave as liquid anion exchangers suitable for the preparation of anion-selective liquid membrane electrodes. Tetraphenylborate and high molecular anionic surfactants such as dodecyl-sulphate, etc., show good selectivity for heavier univalent inorganic cations and are also used in membrane electrodes for other "onium" ions.

The customary type of liquid membrane electrodes is that in which the membrane is composed of a water-immiscible organic solvent containing the ion of interest in the form of an ion-pair with an oppositely charged lipophilic ion. The membrane is interposed between a standard (internal) and the test (external) ion solutions, the voltage being measured for the complete electrochemical cell which comprises the membrane separating internal and external electrolytes, as well as the two (internal and external) reference electrodes. Various assemblies of liquid membrane electrodes have been constructed. In the most used assembly, the organic liquid is held within the pores of a thin disc of about 0.1 μm pore diameter. The inner chamber is filled with the internal aqueous solution in which the inner reference electrode is immersed. This avoids the use of a thick layer of the organic phase; the construction is along the same lines as the Orion Series 92-type liquid membrane electrodes (see p. 2, ref. 17). Porous membranes soaked and saturated with the ion-exchanger material are also often used; Orion liquid membrane electrodes of the Series 93-type contain such membranes (see, for example, Fig. F-5, ref. 18). The electrodes in a third, often used category are also liquid, although they can appear to be solid by use of polymeric supports and gelling components. The construction of those is so that the porous discs of liquid membranes are replaced by a film of plastic membranes (0.2–0.3 mm thick). The membrane film contains the polymeric matrix, the electroactive substance and often also a solvent of polymer and/or a plasticizer. Poly(vinyl chloride) (PVC) as a plastic matrix is the most favoured polymer; the membrane film is usually prepared by evaporating a solvent (tetrahydrofuran or cyclohexanone are most frequently used) from a mixture of PVC, plasticizer and the electroactive substance spread on a glass plate, and is consequently mounted on the polished end of PVC or glass-tubing filled with an inner electrolyte solution containing the ion of interest and completed with an internal reference electrode (see, for example, refs 19–21).

The rôle of the membrane liquid is significant because the nature of the selected organic solvent determines the extraction parameters of an ion-pair (Q^+X^-) and

consequently, the electrode selectivity towards the ion of interest [22–25]. With regard to this point, some interesting studies on membrane electrodes sensitive to some pharmaceuticals were also presented [26–30]. Organic solvents containing nitro groups predominate in all the liquid membrane drug substance-selective electrodes, nitrobenzene being the most popular. Often 2-nitrotoluene, as well as other aromatic nitrocompounds, have been used in liquid membrane electrodes, namely 4-ethyl-nitrobenzene, 4-nitro-*m*-xylene and 4-nitrocumene.

In plastic membrane electrodes, the rôle of plasticizers may be considered analogous to that of organic solvents in liquid membrane electrodes. Above all, these determine the value of the distribution ratio of the particular Q^+X^- ion-pair employed as an ion-exchanger. However, special attention must be paid to their compatibility with the polymer matrix. The most frequently used plasticizers of PVC membranes are those formed by different esters of phthalic acid (e.g. dibutyl-, dipentyl-, dioctyl- and didecyl phthalates), phosphoric acid (tributyl- and tricresyl phosphates) as well as alkyl esters of other acids (sebacates, oxalates, etc.). Another group of plasticizers is represented by compounds containing nitro groups, such as 2-nitrophenyl-, 3-nitrophenyl- and 2,4-dinitrophenyl alkyl ethers, dialkyl esters of both 3-nitrophthalic and 4-nitrophthalic acids, etc. [5]. Examples of some drug substance-selective electrodes are listed alphabetically in Table 1.

Besides the most common construction of the liquid (and plastic) membrane electrodes, another way of preparing polymeric membrane sensors was recommended. The method consists of directly covering the solid contact, thus eliminating the internal electrolyte solution. These "coated-wire electrodes" have become popular because they can be prepared simply by dipping the central conductor into a solution containing dissolved polymer, plasticizer and electroactive substance, and allowing the solvent to evaporate (see refs 80 and 81 for reviews). Some of such electrodes are also listed in Table 1 [50, 51, 61]. As can be seen from the list of references, there is increasing activity in these methods of preparing drug electrodes with membranes containing ion-pairs, especially in China during the last years. Ion-selective field effect transistor (ISFET) techniques were also used [225, 226].

Atypical sensors of pharmaceutical and herbicidal interest are based on crown ethers as neutral carriers incorporated into electrode membranes [246].

Direct Potentiometry with Drug Substance-selective Electrodes

An electrochemical cell consisting of the drug substance-selective measuring electrode and proper reference electrode, can be used to determine the activity or concentration of the ion of interest. Empirical calibration graphs, in which the cell voltage is related to the activity or concentration of the desired ionic compound, are generally used. The calibration graphs are drawn for standard solutions of the analyte, completely dissociated, at concentrations spanning the range to be studied. A typical form of the calibration curve is that given by Nikolskii's equation, and is usually linear in the range of 1 to 5 pX units, where the pX values are calculated as negative logarithms of the desired ion "i" activities, i.e. $pX = -\log a_i$. Furthermore, the calibration can be simplified by plotting the cell voltage values against the negative logarithms of the ion "i" concentrations, i.e. $pX = -\log c_i$. In such cases the calibration curve is not linear and differs from the graph drawn for the activity scale at higher concentrations, where the activity coefficients (y_i, in an equation $a_i = y_i c_i$) are <1. These methods are valid, assuming that there are no interferences due to ion-binding, that the electrode is not able

Table 1
Some drug substance-selective electrodes

Substance(s) determined	Indicator electrode composition	Reference
Acetylcholine	PVC membrane electrode containing acridine orange reineckate as an active material and dioctyl phthalate as plasticizer	31
Acetylcholine and choline	Liquid membrane electrodes with various nitro-arenes containing ion-pairs of acetylcholine or choline with dipicrylamine	73
Aconitine and papaverine	PVC membranes containing ion-pairs of acridine orange with tetraphenylborate or reineckate, plasticized with dioctyl phthalate	32
Amethocaine	Liquid or PVC membranes with amethocaine tetraphenylborate, picrate or reineckate	33
Amylobarbitone	A liquid membrane electrode containing triheptyldodecylammonium salt of amylobarbitone in nitrobenzene solvent mediator	265
Amphetamine	A liquid membrane electrode containing amphetamine octadecylsulphate ion-pair in nitrobenzene	34
Anisodamine	PVC membrane containing bis (2-ethylhexyl) and dinonyl phthalates as plasticizers and anisodamine tetraphenylborate or dipicrylaminate	100
Anisodamine, homatropine, *N*-butylscopolamine	PVC + dibutyl phthalate membranes containing tetraphenylborates of the compounds determined	242
Antazoline	Coated-wire electrode with a PVC membrane containing tetraphenylborate	243
Aspirin	An aspirin-selective electrode	228
Atropine and novatropine	Liquid (2-nitrotoluene) membrane electrodes with atropine or novatropine tetraphenyl- or tetrakis(*m*-chlorophenyl)borates	35
Atropine	Liquid (benzyl alcohol) or PVC (+ dioctyl phthalate) electrodes containing atropine reineckate in both forms of the membranes	105
Atropine	Liquid (nitrobenzene) or PVC (+ dioctyl phthalate) electrodes containing either atropine or potassium tetraphenylborates	36
Atropine	PVC membranes plasticized with dibutyl-, bis(2-ethylhexyl)- or dinonyl phthalates and containing ion-pairs of atropine with tetraphenylborate, dipicrylaminate, reineckate, or tetraiodomercurate(II)	37
Atropine	Liquid membrane electrodes with *p*-nitrotoluene or *n*-octanol mediators and atropinium picrolonate or 5-nitrobarbiturate ion-pairs	219
Barbitone	A liquid (nitrobenzene) membrane electrode containing cetylpyridinium bromide as ion-exchanger	38
Benzalkonium bromide	A PVC membrane electrode containing benzalkonium tetraphenylborate	215
Benzoate, oxalate, salicylate, etc.	Liquid (1-decanol) membrane electrodes containing tricaprylylmethylammonium benzoate, oxalate, salicylate, or other salts	39

Table 1
Continued

Substance(s) determined	Indicator electrode composition	Reference
Benzoic acid	A liquid (1,2-dichlorobenzene) membrane containing tri-*n*-octylmethylammonium benzoate as an electroactive substance	40
Benzylpenicillin	A liquid membrane electrode	218
Berberine	Liquid membrane electrodes containing ion-pairs of berberine with tetraphenyl- or tetrakis(*m*-methylphenyl)borates	42
Berberine	PVC membrane electrodes of both conventional and coated-wire (graphite support) type, containing dibutyl phthalate and berberine tetraphenylborate	41, 213
Berberine	ISFET based on berberine–tetraphenylborate	225
Bupivacaine and mepivacaine	PVC membrane electrodes containing bupivacaine or mepivacaine ion-pairs with dinonylnaphthalenesulphonic acid	223
Carbetapentane	A carbetapentane-selective electrode with phosphotungstate counter ion	206
Chloranilate	Liquid membrane electrodes with different large organic counter cations	245
Chloroquine	A PVC membrane electrode containing chloroquine dinonylnaphthalene-sulphonate ion-pair	196
Chlorpheniramine	PVC membrane electrodes based on tetraphenylborates	44, 45
Chlorpromazine, amitriptyline, propantheline, meperidine	Liquid membrane electrodes containing various ion-pairs of the compounds determined with eosin, tetraphenyl- or tetrakis(*m*-chlorophenyl)-borates dissolved in 2-nitrotoluene or *p*-nitrocumene	46
Cholic acids	Liquid or PVC membrane electrodes based on benzyldimethylammonium cholate in nitrobenzene	48, 266
Cholic acids	A liquid (nitrobenzene) membrane containing tributylcetylphosphonium benzoate	47
Cinchonine	A PVC (+ dibutyl phthalate) electrode with tetraphenylborate counter ion	43
Clobutinol	A PVC (+ dioctyl phthalate) membrane electrode based on clobutinol-tetraphenylborate ion-pair	49
Cloperastine	Cloperastine-dipicrylaminate ion-pair as the active substance	209
Cocaine, methadone, methylamphetamine and protriptyline	PVC membrane electrodes plasticized with dioctyl phthalate and containing the drug dinonylnaphthalene sulphonates	50
Codeine, brucine, quinine, cinchonine	PVC membranes plasticized with dibutyl phthalate and containing potassium tetraphenylborate as an active substance	51
Codeine	A liquid membrane electrode containing codeine-dipicrylaminate ion-pair dissolved in nitrobenzene	99
Dibazol	Liquid or PVC membrane electrodes based on dibazol ion-pairs with various naphthalene sulphonates or tetraphenylborate	235

Table 1
Continued

Substance(s) determined	Indicator electrode composition	Reference
Diphenhydramine	PVC membrane electrodes plasticized with various plasticizers and containing tetraphenylborate, reineckate, tetraiodomercurate(II) or picrolonate as counter ions	52
Diphenhydramine	PVC membrane electrodes of both conventional and coated-wire type based on an ion-pair with tetraphenylborate	137
Diphenhydramine, levamisole, promethazine, berberine, chlorpromazine, procaine, atropine	Liquid membrane electrodes containing triphenylcetylphosphonium tetraphenylborate	53
Dipyrone	PVC membrane plasticized with dibutyl phthalate and containing dipyrone and triheptyldodecylammonium iodide	238
Ephedrine	A liquid membrane electrode containing ephedrine 5-nitrobarbiturate ion-pair in nitrobenzene	211
Ephedrine	A PVC electrode based on ephedrine tetraphenylborate	54
Ephedrine, bamethan, chlorphentermine, oxprenolol, propranolol	PVC electrodes with various plasticizers containing tetraphenylborates of the compounds determined	29
Ephedrine, epinephrine, norepinephrine	Liquid membrane electrodes containing ephedrine flavianate as an active material and 1-octanol as solvent mediator	197
Filcilin	Liquid and PVC membrane electrodes based on tetraphenylborate	190
Glutamates	A liquid (1-decanol) membrane electrode with methyltricaprylylammonium glutamate	55
Histamine	A liquid (nitrobenzene) membrane with histamine tetraphenylborate	56
Hydralazine	A PVC (+ dioctyl phthalate) electrode containing hydralazinium tetraphenylborate	231
Ketamine	PVC membrane electrodes containing ion-pairs of ketamine with tetraphenylborate, silicotungstate, reineckate or picrate and various plasticizers	57
Levamisole	PVC membrane electrodes based on levamisole tetraphenylborate, reineckate, picrate or tetraiodomercurate(II) and various plasticizers	58
Lidocaine	A liquid (nitrobenzene) membrane with dipicrylaminate, or a PVC (+ 2-nitrophenyl octyl ether) membrane with dinonylnaphthalene sulphonate, resp., as a counter ion	184
Lidocaine	A liquid (nitrobenzene) membrane with lidocaine reineckate	205, 247
Lidocaine	A PVC (+ dinonyl phthalate) electrode with tetrakis(3-chlorophenyl)borate as a counter ion	230
Lignocaine, procaine and benzocaine	PVC membrane electrodes containing ion-pairs of cations of anesthetics with tetraphenylborate	232

Table 1
Continued

Substance(s) determined	Indicator electrode composition	Reference
Methacholine, neostigmine, nicotinamide, diphenhydramine, vitamins B_1 and B_6, *p*-aminosalicylic and salicylic acids	Liquid membrane electrodes based on ion-pairs formed by cations of crystal violet or ferroin with dipicrylamine or tetraphenylborate, dissolved in nitrobenzene or 1,2-dichloroethane	59
Methylephedrine and ephedrine	Liquid (nitrobenzene) or PVC (+ dioctyl phthalate) membrane electrodes containing methylephedrine or ephedrine tetraphenylborates	60
Metoclopramide	A PVC (+ dioctyl phthalate) electrode based on tetraphenylborate	210
Moroxydine	Liquid membrane electrodes based on nitrobenzene solutions of moroxydine silicotungstate and other ion-pairs	101
Naftidofuryl	Liquid or PVC membrane electrodes based on ion-pairs of naftidofuryl with dipicrylamine or dinonylnaphthalenesulphonic acid	194
Naphazoline	A PVC membrane containing naphazoline tetraphenylborate and dibutyl phthalate	258
Naproxen	A liquid membrane electrode based on decanol solution of tetraheptylammonium naproxinate	61
Nicotinate	A liquid membrane electrode containing trimethylcetylammonium nicotinate as an active material and decanol as a solvent mediator	62
Nicotine	A liquid membrane electrode based on 2-nitrotoluene solution of nicotine tetrakis(3-chlorophenyl)borate	63
Novocaine	A liquid membrane containing novocaine tetraphenylborate or dipicrylaminate dissolved in nitrobenzene	64
Papaverine, quinine, procaine, pyridoxine, ephedrine, chlorpromazine, thiamine, emetine	Liquid membrane electrodes based on nitrobenzene solutions of tetraphenylborates, alkylsulphates or arenesulphonates of the compounds determined	34
Papaverine, ephedrine, codeine, procaine and others	Liquid (nitrobenzene) or PVC (+ dibutyl phthalate) electrodes containing ion-pairs of alkaloid cations with trioctyloxylbenzenesulphonic acid	233
Phencyclidine	A PVC membrane plasticized with dioctyl phthalate and containing phencyclidine dinonylnaphthalene sulphonate	66
Phenobarbitone	PVC or epoxy-based membrane electrodes containing tricaprylylmethylammonium 5-ethyl-5-phenylbarbiturate in 1-decanol	67
Phenothiazine drugs	PVC (+ 2-nitrophenyl octyl ether) membrane electrodes with tetraphenylborates or dinonylnaphthalene sulphonates of the drugs determined	68
Phenytoin	A PVC membrane based on tricaprylmethylammonium-phenytoin ion-pair	201

Table 1
Continued

Substance(s) determined	Indicator electrode composition	Reference
Pilocarpine	PVC membrane electrodes plasticized with dibutyl phthalate and containing pilocarpine tetraphenylborate or reineckate	69
Promethazine	PVC (+ dibutyl phthalate) electrodes based on ion-pairs with picrolonate or tetraphenylborate	70
Propranolol	Liquid membrane electrodes containing propranolol ion-pairs with various naphthalene sulphonates or tetraphenylborate	224
Quinine	PVC membrane electrodes based on tetraphenylborate counter ion and plasticized with dibutyl phthalate, dibutyl sebacate, nitrobenzene or 2-nitrophenyl octyl ether	71, 72
Salicylate	A liquid membrane electrode (tetrahexylammonium salicylate solution in 1-decanol)	74
Salicylate	A PVC membrane based on ethyl violet salicylate ion-pair	202
Salicylate	An electrode containing trioctylmethylammonium salicylate on conductive epoxy resin	244
Strychnine	Liquid membrane electrodes based on ion-pairs of strychnine with picrolonate or tetrakis(3-methylphenyl)borate	75, 76
Succinylcholine, hexamethonium, decamethonium	PVC membrane electrodes containing ion-pairs of the bisquaternary drugs with triphenylstilbenylborate and plasticized with 2-nitrophenyl octyl ether, dioctyl phthalate and other solvents	102
Sulphisomidine and sulphamerazine	Liquid membranes based on nitrobenzene solutions of ion-pairs of the tris(bathophenanthroline)iron(II) with the sulpha drugs	77
Tetracycline and related compounds	PVC membrane electrodes	227
Tetrahydropalmatine	PVC membranes based on tetrahydropalmatine picrolonate or tetraphenylborate and plasticized with dibutyl phthalate	78
Thalidasine	PVC(+ dibutyl phthalate) electrode containing tetraphenylborate as counter ion	229
Thiopentone, phenobarbitone, amobarbitone, phenytoin, salicylate, etc.	PVC electrode containing cetyltrioctylammonium iodide and dibutyl phthalate with inner graphite contact	237
Trimethoprim	PVC membrane electrodes based on ion-pairs with tetraphenylborate or silicotungstate	236, 248
Vanillin after oxidation to vanillic acid	PVC membrane vanillate ion-selective electrode	216
Vitamin B_1 (thiamine)	PVC membrane electrodes based on tetraphenylborate and dibutyl phthalate	199, 217
Vitamins B_1 and B_6	Liquid membrane electrodes based on 1,2-dichloroethane solutions of ion-pairs with tetraphenylborate	79
Vitamin B_6 (pyridoxine)	PVC membrane electrodes of conventional or coated-wire type based on pyridoxine tetraphenylborate or dipicrylaminate	192, 198

to sense ions other than the relevant ions in the test solution, and that the activity coefficients in both the standard and test solutions are approximately the same.

Other techniques involve measurements by standard addition and subtraction methods. The advantage of these techniques is that measurement of the total concentration of the complexed and uncomplexed ions can be made, even in very complicated systems. In addition, the measurements can be made even in solutions having widely varying ionic strength.

Practically any of the electrodes listed in Table 1 can be used for direct potentiometric determination of the desired drug content. The response is usually fast and linear up to concentrations of 10^{-5} mol dm^{-3}. Irrespective of the membrane composition, electrode ageing has a marked effect on the slope of the calibration graph: the initial slope is usually nearly Nernstian but in several weeks or months of normal use, the slope decreases significantly. This must be allowed for by calibrating the slope before each series of measurements because the slope must be accurately known for all direct potentiometric techniques.

Indirect determinations of alkaloids based on direct potentiometry were also presented. For example, strychnine, papaverine, quinine and cocaine were determined after reaction with standard sodium picrate solution. After the ion-pair precipitation was completed, the excess picrate concentration was measured with a picrate-selective electrode [82].

Techniques of direct potentiometric measurements are quick and ion-selective electrodes are widely applicable to many drug substances (Table 1). However, the errors in direct potentiometry are usually much larger than those for potentiometric titrations. If the usual deviation of the potential measurements of ± 1 mV at normal laboratory temperature is assumed, the resultant relative error in direct potentiometric determination is $\pm 4\%$ for univalent, or $\pm 8\%$ for bivalent ions [136].

Potentiometric Titrations Based on Ion-pair Formation

In contrast to direct potentiometry, the potentiometric titration technique offers the advantage of high accuracy and precision, though at the cost of increased time demands and increased consumption of chemicals used as titrants. A further advantage is that the potential break at the titration end-point must be well defined, but the slope of the electrode response need be neither reproducible nor Nernstian and the actual potential value at the end-point is of secondary interest. This makes possible the use of simplified sensors, the membranes of which can be prepared from polymer solutions containing no active material. Higuchi *et al.* [83] have shown that nearly any organic plastic matrix of limited hydrophilicity can be used as the gelling component of the membrane, the selection being primarily guided by its compatibility with the desired plasticizer; the liquid components were chosen for their ability to solvate the particular ions of interest. Similar sensors have also been used by Hoke and Collins [103] and Dilley [104].

Similar sensors of the coated-wire type have been studied [84, 90, 91]. An ordinary aluminium conductor with thick PVC insulation, which eliminates mounting the wire into a tube has been recommended [84] for preparing coated-wire electrodes. Such sensors are very cheap and may easily be constructed even from waste materials [85]. The preparation of the simple coated-wire type elements has recently been described, and instructions for their use have been given [86].

Potentiometric titrations in which similar simple sensors were used in determinations

of drug substances are chronologically listed in Table 2. In these titrations, a cationic (Q^+) or anionic (X^-) species is titrated with an oppositely charged titrant (X^- or Q^+); if either the substance determined or the titrant (or both) has adequate lipophilic character, precipitation of the poorly soluble ion-pair occurs in water,

$$Q^+ + X^- \rightleftarrows QX.$$

However, as shown above, the same ion-pairs can be employed as active substances for liquid membrane-type electrodes because of their good extractability into organic water-immiscible solvents. Therefore, if the simplified electrode with a membrane prepared from a plasticized plastic matrix only, is immersed into a stirred aqueous suspension of the QX ion-pair, the organic solvent (plasticizer) becomes gradually saturated with the ion-pair, the concentration being given by

$$[QX]_{org} = K_{ex}(QX)[Q^+]_{aq}[X^-]_{aq} = K_{ex}(QX).K_s(QX),$$

where $K_{ex}(QX)$ and $K_s(QX)$ are the stoichiometric extraction constant and the solubility

Table 2
Simple sensors for ion-pair formation-based titrations of drug substances

Substance(s) determined	Indicator electrode type	Reference
Diphenhydramine, dextromethorphan	Conventional (with inner electrolyte and inner reference electrode), PVC + *N*,*N*-dimethyloleamide membrane	83
Diphenhydramine, dextromethorphan, tetraalkylammonium salts	Conventional, PVC + *N*,*N*-dimethyloleamide or PVC + dioctyl phthalate membranes	87
Dextromethorphan alone or in the presence of Na^+ or Et_3NH^+	Conventional, PVC + *N*,*N*-dimethyloleamide membrane	88, 89
Methadone in urine	Coated-wire (silver/silver chloride support), PVC + dioctyl phthalate membrane	90
Procyclidine, cyclizine and diethylcarbamazine	Coated-wire (graphite), PVC + bis(2-ethylhexyl) phthalate membrane	91
Acetylcholine, aconitine, procaine, Septonex, cetylpyridinium bromide, etc.	Coated-wire (various supports), PVC or poly(vinyl butyral) (PVB) membranes containing various plasticizers	84, 96
Aromatic amines in form of arenediazonium salts	Coated-wire (aluminium conductor), PVC membrane plasticized with 2-nitrophenyl 2-ethylhexyl ether or some of eight other liquids	92
Cationic surfactants used as disinfectants	Coated-wire (aluminium), PVC or PVB membranes containing various plasticizers .	93
Cationic triarylmethane dyes used as disinfectants	Coated-wire (aluminium), PVC + 2-nitrophenyl 2-ethylhexyl ether or PVC + tricresyl phosphate membranes	94
4-Aminoacetanilide and other aromatic amines in form of diazonium salts	Coated-wire (aluminium), PVC membrane plasticized with either 2-nitrophenyl 2-ethylhexyl ether or 2-nitrophenyl *n*-octyl ether or dioctyl 3-nitrophthalate	95

Table 2
Continued

Substance(s) determined	Indicator electrode type	Reference
Cetylpyridinium chloride	Coated-wire (graphite), PVC + dioctyl phthalate membrane	97
Septonex in nasal and eye drops, pilocarpine, ethylmorphine, homatropine and cinchocaine in eye drops	Coated-wire (aluminium), PVC membranes plasticized with either 2,4-dinitrophenyl *n*-octyl ether or dioctyl phthalate	86
Procaine, trimecaine and xylocaine in parenteral preparations	Coated-wire (aluminium), PVC membranes plasticized with either 2,4-dinitrophenyl *n*-octyl ether or dioctyl phthalate	98
Surfactants used as disinfectants and other examples	Coated-wire (aluminium), prepared from plasticized pure PVC or waste plastics	85
Fenomerbor	Potassium ion-selective electrode based on tetraphenylborate	193
Atropine, cinchocaine, homatropine, scopolamine, pilocarpine in eye drops	Coated-wire (aluminium), PVC + 2,4-dinitrophenyl *n*-octyl ether membrane	220
Tetraalkylammonium salts, cationic surfactants and triphenylmethane dyes used as disinfectants	Coated-wire (graphite support), PVC membranes plasticized with either dibutyl or diheptyl phthalates	222
Tetraalkylammonium salts	Coated-wire (copper wire covered with a graphite + polystyrol paste and coated with a PVC + tricresyl phosphate membrane containing tetrabutylammonium tetraarylborates	250
Brucine, atropine	Coated-wire (aluminium) with plasticized PVC membranes; nine different plasticizers were compared: dibutyl-, diamyl-, bis(ethylhexyl)-, dinonyl- and didecyl-phthalates, 2,4-dinitrophenyl *n*-octyl ether, dibutyl maleinate, tricresyl- and xylenyl phosphates	251
Berberine, propantheline, benzalkonium chloride, tetrabutylammonium iodide	Coated copper wire	204
Eleven drugs containing piperazine, piperidine or pyrrolidine rings	Coated-wire (graphite), PVC membranes plasticized with a mixture of dioctyl phthalate and nitrobenzene with addition of sodium tetraphenylborate	153
Sulphated glycosaminoglycans, Heparon, Heparin; back-titration of excess Septonex	Coated-wire (aluminium) with a PVC membrane plasticized with 2,4-dinitrophenyl *n*-octyl ether	253
Mephenoxalone hydrolysis products	Coated-wire (aluminium), PVC + 2,4-dinitrophenyl *n*-octyl ether membrane	254
Brucine, atropine	Conventional pH glass electrode coated with a plasticized PVC membrane	257

All procedures involve the titrations with sodium tetraphenylborate except for ref. 204 in which potassium iodomercurate titrant was used.

product of QX, respectively. This $[QX]_{org}$ concentration can be seen as a number of ion-exchanging places in the membrane, although a surface adsorption can also take place. That is why commercial liquid and/or plastic membrane electrodes sensitive to ions other than those to be determined can also be used to monitor ion-pair formation-based titrations (Table 3).

Table 3
Commercially available ion-selective electrodes used in ion-pair formation-based titrations of compounds of pharmaceutical interest

Substance(s) determined	Electrode(s)	Titrant(s)	Reference
Aconitine, apomorphine, arecoline, brucine, papaverine, physostigmine, pilocarpine, strychnine, yohimbine	Crytur 19–15 potassium	NaTPB	106
Protonated organic bases, cationic dyestuffs used as disinfectants, etc.	Crytur 19–15 potassium	NaTPB	107
Univalent cations (a review)	Crytur 19–15 potassium	NaTPB	108
Quaternary ammonium compounds of pharmaceutical significance	Orion 93–19 potassium	NaTPB	109
Strychnine, brucine, cinchonine, atropine, yohimbine, quinine, pilocarpine, protonated organic bases, cationic dyestuffs	Orion 93–05 fluoroborate, 93–81 perchlorate, 93–07 nitrate, 93–19 potassium, 94–06A cyanide	NaTPB	110
Aqueous pharmaceutical formulations of alkaloids	Crytur 19–15 potassium	NaTPB	111
Procaine, diphenhydramine, chlorpheniramine, cationic dyes	Orion 93–05 fluoroborate, 94–06A cyanide	NaTPB	112
Cationic surfactants used as disinfectants	Orion 93–81 perchlorate	NaTPB	113
Various nitrophenols and other nitro group-containing anionic compounds	Orion 93–81 perchlorate	TPPA	127
Various nitrophenols and other anionic compounds used pharmaceutically	Orion 93–05 fluoroborate	CTAB, CPC	128
Picrate and other organic anions	Orion 94–06 cyanide, 94–53 iodide, 94–16 silver/sulphide and others	CPC, CTAB, CTAC and other cationic compounds	129
Benzododecinium bromide (Ajatin)	Crytur 20–25 calcium, 05–25 fluoroborate, 07–25 nitrate, 81–25 perchlorate	NaTPB (KBF_4, $KClO_4$, K hydrogen phthalate, Na salicylate, Na benzoate)	252

NaTPB — sodium tetraphenylborate, TPPA — 1,2,4,6-tetraphenylpyridinium acetate, CTAB — cetyltrimethylammonium bromide, CTAC — cetyltrimethylammonium chloride, CPC — cetylpyridinium chloride.

With regard to titrants, practically the same compounds used as lipophilic counter ions in liquid membranes can be selected. Drug substances which are present in their cationic forms (salts of alkaloids, cationic disinfectants, etc.) are usually titrated with sodium tetraphenylborate [5]. This compound is exceptional among anionic titrants and is unlikely to be replaced by others, except for some other tetraarylborates, such as sodium tetrakis(3-trifluoromethylphenyl)borate [114], sodium tetrakis(α-thienoyl)borate [115], etc., which are not, however, commercially available. Titrations with sodium tetraphenylborate may also be monitored with specially pretreated silver [116–118] and mercurized platinum electrodes [119–122] as well as some solid-state silver sulphide-based membrane electrodes [110, 112, 123]. Sodium tetraphenylborate solutions for titrations with ion-selective electrodes can advantageously be standardized against thallium(I) nitrate or sulphate as primary standards [124]. Any PVC-matrix membrane electrode can be used to monitor the end-point which is characterized by a very sharp potential break [92, 124, 125]. The standardization against tetraphenylarsonium chloride has also been recommended [126].

The use of other anionic titrants such as sodium picrate, sodium 3,5-dinitrosalicylate, sodium dodecylsulphate, etc., does not have any significant advantage. The choice of picrolonic acid solution as a titrant has made the selective determination of strychnine in the presence of other alkaloids possible: the reaction of many amines and alkaloids with picrolonic acid does not lead to the formation of precipitates or give precipitates much more soluble than that of strychnine. In the procedure recommended [75], an aliquot of the alkaloid mixture containing strychnine is adjusted to pH 4–7 and titrated with a 0.005 M standard solution of picrolonic acid for strychnine, followed by titration of the total alkaloid with 0.005 M standard sodium tetraphenylborate in a separate aliquot. The method was tested on binary alkaloid mixtures containing strychnine and pilocarpine, atropine or cinchonine, and acceptable recoveries were obtained.

Anionic compounds are analogously titrated with cationic titrants, however, no cationic reagent corresponds to sodium tetraphenylborate in its exceptional quality. The choice of a suitable titrant for substances of anionic character is therefore less straightforward. Various quaternary ammonium and pyridinium salts have been the most frequently used (see ref. 5). Among anionic compounds of pharmaceutical significance, various nitrophenols used as disinfectants have been determined by titrations with 1,2,4,6-tetraphenylpyridinium acetate [127], cetyltrimethylammonium bromide, cetylpyridinium chloride and other tetraalkylammonium salts [128, 129] as well as with crystal violet [130, 131], tetraphenylarsonium chloride [132] or even silver nitrate in the presence of thiourea [133].

Potentiometric Titrations Based on Complex Formation

Organic molecules containing atoms such as nitrogen, oxygen, sulphur, etc., can donate pairs of electrons, i.e. they are electron donors. Therefore, they can form complexes with metal ions (M), which are electron acceptors, in which they are bound as unidentate or multidentate ligands (L). Depending on other groups of the organic molecule, these complexes can be either charged or neutral, i.e. either soluble or insoluble in water. Thus, generally the chemical reaction can be considered to be

$$n\,\mathrm{L} + m\,\mathrm{M} \rightleftarrows \mathrm{M}_m\mathrm{L}_n$$

(charges are omitted).

If the equilibrium constant of this reaction (a stability constant of the M_mL_n complex) is sufficiently high, these compounds can be determined by titration with solutions of metal salts used as titrants. Experience has shown that the above reaction between M and L is affected by competitive side reactions, caused by the presence of various substances usually present in the solution analysed, i.e. other ligands from buffer constituents, counter ions, etc., and especially by the pH value. Thus, the success of such titration depends on the value of the conditional stability constant of the complex M_mL_n. For many complexes such conditions can be found and the complex formation reaction can well be adapted to titrimetric determination.

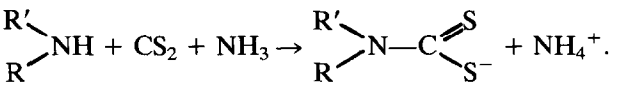
It is self-evident that titrations in which solutions of metal salts are used as titrants can be followed with appropriate metal ion-selective electrodes. Many pharmaceuticals can be titrated with solutions of copper, lead, mercury, silver, and other metal ions. Some examples of the use of ion-selective electrodes for monitoring such titrations are given in Table 4.

Table 4
Complex formation-based titrations of some compounds of pharmaceutical interest

Substance(s) determined	Titrant	Electrode selective to	Reference
Amides and substituted uracils	Ag^+	Silver/sulphide	148
Amines	Ag^+	Silver/sulphide	203
Amino acids	Ag^+	Silver/sulphide	148
	Hg^{2+}	Silver/sulphide or mercury	149, 150
Aminocarboxylic acids	Cu^{2+}	Copper	135, 142
NTA, EDTA, DCTA	Cd^{2+}	Cadmium	138
NTA, EDTA, DCTA, HEDTA, EGTA	Ca^{2+}	Calcium	141
Aminophenols, aliphatic diamines and polyamines	Cu^{2+}	Copper	161–163
Ampicillin and amoxycillin after enzymic or alkaline hydrolysis	Cu^{2+}	Copper	188
Catechols	Pb^{2+}	Lead	157, 158
8-Chlorotheophylline	Ag^+	Silver	214
Citrate (citric acid)	Cu^{2+}	Copper	135, 159
Cysteine	Ag^+	Silver/sulphide	148
Cysteamine, cystaphos	Hg^{2+}	Silver/sulphide	151
Dyes containing chelating groups	Cu^{2+}	Copper	191
Glutamic, aspartic and aminoacetic acids	Cu^{2+}	Copper	164
Guanidine derivatives	Cu^{2+}	Copper	140
Methimazole	Cu^{2+}	Copper	144
Oxalate and soaps	Ca^{2+}	Calcium	141
Oxalate, diethyldithiocarbamate, NTA, diethylenetriaminepentaacetic acid	Pb^{2+}	Lead	160
Oxalate	Pb^{2+}	Lead	156
Penicillamine	Pb^{2+}	Lead	143
Phenylthiourea	Ag^+	Silver/sulphide	147
Phenylhydrazine	Cu^{2+}	Copper	152
Phenytoin	Ag^+ or Cu^{2+}	Silver or copper	234
8-Quinolinol and its derivatives	Cu^{2+}	Copper	135
8-Quinolinol and derivatives, *N*,*N*-diethyldithiocarbaminate and others	Cd^{2+}	Cadmium	138
Sulphonamides	Ag^+	Silver	155
Sulphonimide	Ag^+ or Cu^{2+}	Silver/sulphide or copper	154
Thioamides	Ag^+	Silver/sulphide	187
Thiobarbituric acid derivatives	Ag^+ or Cu^{2+}	Silver or copper	134, 221
Thiouracil, methylthiouracil	Ag^+	Silver/sulphide	145
Thiourea	Ag^+	Silver/sulphide	146
as-Triazines	Ag^+	Silver/sulphide	139

Many drug substances can also be determined after the reaction with a metal ion, the excess of which is then back-titrated with EDTA. For example, a method for the determination of total penicillins in pharmaceutical preparations is based on desulphurization with potassium plumbite, whereby one mole of lead sulphide is formed per mole of penicillin; the excess of lead(II) is titrated with EDTA with the use of a lead ion-selective electrode [165]. A similar method was developed for determination of thiambutosine [166]. Sulphonamides may be directly titrated with mercury(II) salts, however, the use of an excess of mercury(II) for completely precipitating the sulpha-drugs and back-titration of the excess metal ion with EDTA gives the most satisfactory results [167]. Broxyquinoline (directly) and brobenzoxaldine (after alkaline hydrolysis) react with copper(II) sulphate as a precipitant, the excess of which is titrated with EDTA [239].

Another procedure involves the derivatization of the substance to be determined. For example, secondary amines and their salts react with carbon disulphide yielding dialkyldithiocarbamic acid quantitatively, regardless of the dissociation constant of the amine, according to



The reaction is done in the presence of ammoniacal copper sulphate solution yielding copper dialkyldithiocarbamate. The excess copper(II) is titrated with either EDTA or sodium diethyldithiocarbamate, the titration being monitored with a copper ion-selective electrode [168].

Miscellaneous

A conversion of the drug substance to be determined into a product, the concentration of which is measurable with an ion-selective elecrode or which can be titrated using ion-selective electrodes, can also be utilized. Thus, the hydrolysis of nicotinamide in alkaline solution yields ammonia; an ammonia gas-sensing electrode is then used to follow the gas formation [169]. Another application of the ammonia-selective electrode is the determination of meprobamate after decomposition with acid [170]. Determination of *N*-ethyl- and *N*,*N*-diethylnicotinamide by acid hydrolysis followed by potentiometric measurements with alkylamine electrodes has also been described [207]; the electrode was prepared by displacing the inner solution of the commercial ammonia electrode with 0.05 M solutions of ethylammonium or diethylammonium chlorides.

N-Acetyl-L-cysteine, glutathione and D-penicillamine reduce iodine to produce iodide ions in acidified solutions; the iodide is then determined by titration with silver nitrate monitored with an iodide-selective electrode [171]. Similarly, nitrendipine reacts with iodine, releasing iodide ions, the concentration of which can be determined potentiometrically using a cyanide-selective electrode [241]. Following mineralization, five fluorine-containing synthetic glucocorticosteroids were determined by measuring their fluorine content; a potentiometric titration with lanthanum(III) nitrate against a fluoride-selective electrode was found to be the most precise method [260]. Other examples are given in specialized texts [7, 9].

Traditional titration with sodium nitrite titrant is still often used to determine compounds containing primary amino-groups on the aromatic ring, the end-point being monitored with a platinum indicator electrode or other sensors [65]. This method, applied to the determination of sulphonamide pharmaceuticals [172, 173], is rapid and the results are in good agreement with official methods of analysis. Methoclopramide [195], benzocaine and procaine [172] have also been determined by this method. Furthermore, substituted arenediazonium salts, obtained in titrations with sodium nitrite, can be used as titrants in determinations involving azo-coupling reactions [174]. These titrations can be followed with a plastic membrane-based ion-selective electrode, preconditioned in a stirred aqueous suspension of the appropriate arenediazonium tetraphenylborate [175, 176]. Various aromatic amines, phenols and compounds containing active methylene groups have been titrated with 4-methyl-, 4-bromo-, or 4-nitrobenzenediazonium chloride solutions [175]. Recently, more lipophilic arenediazonium salts derived from 1-aminonaphthalene, 1-amino-4-bromonaphthalene, 1-amino-4-nitronaphthalene and 1-amino-9,10-anthraquinone were tested as titrants [176]; 4-bromo-1-naphthalenediazonium chloride seemed to be the most widely applicable reagent. Some pharmaceutically related compounds such as 8-quinolinol, resorcinol, phloroglucinol, quercetin, apomorphine, etc., have also been determined [176].

Compounds that react slowly with arenediazonium salts can be determined by back-titration. When 1-naphthalene- or 4-bromo-1-naphthalenediazonium chloride is used, the excess is back-titrated with either sodium tetraphenylborate or 2,4-diaminotoluene [177]. Indirect determination has also been used for secondary amines, which react with arenediazonium ions to form triazenes [178]. Aminobenzoic acids and other compounds containing solubilizing groups react with sodium nitrite to form arenediazonium salts of ampholytic character. The determination is then based on the reaction of the above salts with 1-phenyl-3-methyl-5-pyrazolone, the excess of which is titrated with standardized 4-bromo-1-naphthalenediazonium chloride solution [179]. The method can be used also for benzocaine and sulphamethoxydiazine, but is not convenient for sulphanilamide and sulphacetamide because of the time-consuming nature of the analysis.

Kinetic methods have also been applied to the analysis of drug substances. The determination of creatinine in urine with a picrate-selective electrode was even recommended as a laboratory experiment for educational purposes [185]. Kinetic methods often have advantages over equilibrium techniques, especially when mixtures of closely related compounds, compounds that react slowly, or catalytically-acting compounds are to be analysed. The selectivity and the sensitivity of kinetic methods of analysis combined with the selectivity and sensitivity of ion-selective electrodes provide an excellent and versatile combination, which may lead to totally new analytical schemes. A review paper dealing with this subject matter has recently been published [186].

Many substances of pharmaceutical interest may be determined by the use of biocatalytic membrane electrodes, in which a biocatalyst (enzyme, tissue, bacteria) is immobilized at the surface of an electrochemical sensor. The biocatalyst serves to catalyse a reaction that involves the substrate of interest while either consuming or producing a species that is measured by the electrochemical sensor. For example, acetylcholine, urea or penicillin G can be determined using sensors in which the enzyme layer (acetylcholine esterase, urease, or penicillinase, respectively) covers the membrane of a conventional pH glass electrode [249]. Urea can also be determined in solution by using immobilized urease on an antimony electrode [264]. The determination of

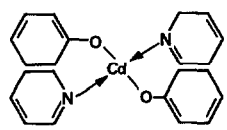
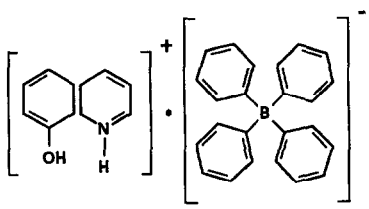
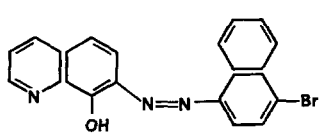
penicillin G was carried out with an enzyme sensor containing penicillinase adsorbed on the surface of a PVC-based coated-wire electrode [226, 240]. A potentiometric biosensor for riboflavin (vitamin B_2) was also described [208].

Numerous biochemical sensors work also on an amperometric principle; the sensors and methods developed recently have been included into general reviews [15, 182, 183, 200, 212, 255, 256, 261–263]. The short lifetime of the sensors is one of the reasons why they are not widely used. This can be overcome by preparation of synthetic enzymes [267] and this may be the strategy for future research work.

Conclusions

The introduction of ion-selective electrodes into pharmaceutical analysis has significantly contributed to the increase in the number of compounds that can be determined

Table 5
Schematic presentation of different methods used for potentiometric titrations of 8-quinolinol with ion-selective electrodes

Titrant/Medium	Indicator electrode and titration curve	Product
(A) Cadmium nitrate; Borate pH 9.1 buffer	Solid-state cadmium selective; Plastic membrane electrodes	
(B) Sodium tetraphenylborate; Hydrochloric acid	Arenediazonium ions selective plastic membrane	
(C) 4-Bromo-1-naphthalenediazonium chloride; Britton-Robinson pH 10 buffer		

In the diagrams, the potential changes are marked by an ordinate scale E equal to 100 mV, but the titrant volumes are different: $V(A)$ = 1 ml, $V(B)$ = 4 ml, or $V(C)$ = 2 ml, resp. For other details see refs 138, 107 and 176.

potentiometrically. The simplicity of the apparatus and measuring techniques using ion-selective electrodes has made their application a rapidly growing field. Suitably combined with known chemical reactions, they may also offer some interesting possibilities for drug analysis. Thus, for example, at least three methods can be used for potentiometric titrations of 8-quinolinol (Table 5). The first involves the titration with a metal ion salt yielding an insoluble complex, the titration being monitored with an appropriate metal ion-selective electrode [134, 135, 138]. In the second method, based on the ion-pair formation principle, the substance is converted to its 8-hydroxyquinolinium cation by addition of dilute hydrochloric acid, and titrated with sodium tetraphenylborate [107]. The third titrant which can be used is an arenediazonium salt yielding irreversibly an azo-dye [175, 176]. Both the second and third types of titration can be monitored with plastic membrane-based electrodes.

Amino acids can be determined by potentiometric titration with metal ion salts [148–150] or by direct potentiometry with a simple copper-wire electrode, which has been shown to respond to the anionic form of the α-amino acid [180]. Procaine can be titrated in the form of the procainium cation with sodium tetraphenylborate [51, 84, and other refs], or with sodium nitrite [172] to form its diazonium salt, which subsequently can be coupled with 1-phenyl-3-methyl-5-pyrazolone, or titrated with tetraphenylborate again [181]. Similarly, alternative methods can be used to determine many other drug substances. This can be utilized advantageously to analyse a pure substance, as a choice of the methods may yield one of high precision. To determine a substance in the presence of others, the choice of methods may yield a procedure that is specific for the analyte.

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[*Received for review 3 January 1989*]