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Potentiometric titration of thiols, cationic surfactants and halides using a solid-state silver–silver sulphide electrode

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Abstract: A rugged, low resistance silver–silver sulphide solid-state electrode for determining pharmaceuticals as authentic samples or in dosage forms by potentiometric titration is described. Sodium tetraphenylborate, mercury(II) acetate and silver nitrate (0.01 M) were employed as titrants in the analysis of cationic surfactants (cetylpyridinium chloride, benzethonium chloride, benzalkonium chloride and chlorhexidine salts), antithyroid drugs (methimazole and propylthiouracil) or sodium halides respectively.

Keywords: *Potentiometric titration; ion-selective electrode; antithyroid drugs; quaternary ammonium salts; chlorhexidine salts; halides.*

Introduction

The use of the silver sulphide membrane electrode for determining thiols has been reviewed [1]. In previous papers the present authors have described the use of a silver electrode (with different pretreatments) in the direct potentiometric titration of antithyroid drugs or antiseptic quaternary ammonium compounds [2–4], and a new technique for preparing solid-state electrodes from a mixture of silver powder and silver halide [5]. The low electrical resistance and the ruggedness of the latter type of pellet electrode lacking an inner reference electrode are exploited for the preparation of a silver–silver sulphide electrode in the present work. This electrode has been applied to the assay of antithyroid thiols, cationic surfactants (quaternary ammonium or chlorhexidine salts) and halides with the three different titrants mercuric acetate, sodium tetraphenylborate and silver nitrate respectively.

Experimental

Drugs and formulations

Methimazole U.S.P., methimazole tablets (5 mg), propylthiouracil B.P., cetylpyridinium chloride B.P., cetylpyridinium chloride disinfectant solution (0.2%), benz-

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ethonium chloride U.S.P., benzethonium chloride disinfectant solution (0.1%), benzalkonium chloride U.S.N.F., benzalkonium chloride hard contact lens solution (0.01%), chlorhexidine gluconate solution B.P., chlorhexidine acetate B.P., chlorhexidine gluconate mouth rinse (0.2%), sodium chloride Eur. P., sodium bromide Eur. P. and sodium bromide injections (25 mg) were obtained through normal commercial channels.

Reagents

Mercury(II) acetate (0.01 M) stabilized by adding glacial acetic acid (0.12% v/v), 0.01 M sodium tetraphenylborate (TPB) stabilized at pH 8–9 by adding a little 1 M sodium hydroxide, 0.01 M silver nitrate, 0.025 M borate, 0.07 M phosphate buffer (pH 7.2), 0.2 M acetate buffer (pH 3.4), 0.6 M nitric acid, octoxynol 9 U.S.N.F. (Triton X-100) 0.2% m/v and iron(III) nitrate were used. Reagents were of analytical grade unless otherwise stated.

Silver–silver sulphide electrode preparation

Moist, purified silver chloride was added to 1 g/ml potassium hydroxide solution and digested for 1 h at 90°C with continuous stirring. The resulting silver oxide in the hot alkaline solution was reduced with 2 M glucose, added dropwise until a light grey powder of silver was obtained. After thorough washing with distilled water, the powder was dried and passed through a 5 μm mesh sieve. Sodium sulphide (0.1 M) was then slowly dropped into a slurry of the silver powder and 0.1 M silver nitrate ($Ag:Ag^+$ ratio ranging from 1:4 to 1:1) until an excess of sulphide was present. The precipitate was thoroughly washed with distilled water and dried at 110°C. A pellet was made by pressing about 2 g of the precipitate in a pellet die (as used for potassium bromide discs) using a hydraulic bench press (Beckman 00–25). Over the silver–silver sulphide pellet about 0.3 g of silver powder was pressed in the same manner in order to obtain an easy surface for soldering. A cable was welded onto the silver and the pellet was fixed with epoxy resin at the end of some plexiglass tubing (Fig. 1). The outer face of the pellet was smoothed with emery paper and then polished with wet chromium(III) oxide.

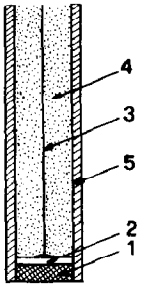

Figure 1
Schematic of solid-state silver–silver sulphide electrode: 1, heterogeneous solid-state pellet; 2, pressed silver powder; 3, welded lead; 4, epoxy resin; 5, electrode body (plexiglass).

Apparatus

Titrations were recorded by means of a Mettler automatic titrator equipped with the equilibrium titration control module DK 15 or with the slope-fitting module DK 11. Titrants were delivered from 2 or 5 ml piston burettes calibrated in equal increments of 0.002 or 0.005 ml, respectively. Potentials were referred to a mercury(I) sulphate electrode. Prior to each titration the surface of the indicating electrode was renewed by polishing it with a suede cloth impregnated with chromium(III) oxide.

Analysis of pure samples

A suitable and accurately measured aliquot of an aqueous working solution of the drug was placed in a potentiometric cell (Metrohm EA 875–20) and made up to 10.0 ml using sufficient pH adjuster (in the case of antithyroid drugs) or water. For assaying cationic surfactants or halides, either 1 ml of acetate buffer or 1 ml of 0.6 M nitric acid was then added, respectively. In the case of chlorhexidine salts, 1 ml of 0.2% m/v octoxynol 9 was also added. The electrode system was dipped into the well-stirred solution, then about 40% of the theoretically necessary volume of 0.01 M titrant was delivered. After waiting until a steady potential had been reached, the titration was automatically recorded. For each drug the conditions regarding pH adjuster, titrant and amount taken are presented in Table 1.

Each ml of 0.01 M titrant is equivalent to 2.283 mg of methimazole, 3.405 mg of propylthiouracil, 3.580 mg of cetylpyridinium chloride, 4.481 mg of benzethonium chloride, 3.600 mg of benzalkonium chloride, 4.489 mg of chlorhexidine gluconate, 3.128 mg of chlorhexidine acetate, 0.584 mg of sodium chloride and 1.029 mg of sodium bromide.

Analysis of commercial dosage forms

For each pharmaceutical dosage form the exact amount of active ingredient taken is presented in Table 2. The pH adjuster and titrant were those employed for the corresponding pure drug. For the analysis of methimazole tablets, ten tablets were weighed and finely powdered. A sample of powder equivalent to 25 mg of methimazole was weighed in a volumetric flask, made up to 50.0 ml with 0.025 M borate and stirred magnetically for 10 min. The solution was suction-filtered through a No. 4 sintered-glass crucible and 10.0 ml of the filtrate transferred to a potentiometric cell. The electrode system was then immersed and the titration carried out. In the analysis of cationic surfactant antiseptic formulations, a suitable aliquot of solution was pipetted into a potentiometric cell and the general procedure for the pure drug was followed. For the benzalkonium chloride hard contact lens solution, 1 ml of 2 M acetate buffer was used, since a higher buffer capacity was required to maintain the pH of the test solution at about 3.5. For bromide analysis a suitable volume of the sodium bromide injection (nominal concentration 12.5 mg/ml) was diluted to yield a theoretical concentration of 0.5 mg/ml. Exactly 5 ml of this solution, 5 ml of distilled water and 1 ml of 0.6 M nitric acid were pipetted into a potentiometric cell. The procedure thereafter was identical to that described above.

Results and Discussion

The results of the quantitative assays presented in Tables 1 and 2 clearly demonstrate the utility of the direct potentiometric method for the analysis of drug compounds and commercial dosage forms without interference from other ingredients. Investigations of electrode performance showed that the percentage of metallic silver in the precipitate was not critical. Electrodes employing pellets prepared from mixtures with the $Ag:Ag^+$ ratio ranging from 1:4 to 1:1 all exhibited identical behaviour. Moreover, stirring efficiency was not critical for obtaining reasonably reproducible electrode potential values on repetitive measurement. Automatically recorded titration curves are presented in Fig. 2; the end-points were taken as the volumes corresponding to the maximum $\Delta E/\Delta V$ values.

Table 1
Potentiometric titrations of pure drugs

Compound	pH adjuster	Titrant used (0.01 M)	Quantity taken (mg)	Average recovery, % (± S.D., $n = 12$)
Methimazole*	0.025 M borate	Mercury(II) acetate	2–5	100.3 (0.7)
Propylthiouracil†	0.07 M phosphate buffer	Mercury(II) acetate	2–6	100.1 (0.4)
Cetylpyridinium chloride	0.2 M acetate buffer	Sodium TPB	2–8	100.3 (0.2)
Benzethonium chloride	0.2 M acetate buffer	Sodium TPB	2–6	100.4 (0.7)
Benzalkonium chloride	0.2 M acetate buffer	Sodium TPB	1–4	101.4 (0.9)
Chlorhexidine gluconate	0.2 M acetate buffer	Sodium TPB	1–4	101.8 (1.4)
Chlorhexidine acetate	0.2 M acetate buffer	Sodium TPB	1–4	98.6 (0.9)
Sodium chloride–sodium bromide mixtures	0.6 M nitric acid	Silver nitrate	0.4–2 0.6–3	100.4 (0.3) 99.7 (0.3)

* Working solution prepared in 0.025 M borate.
† Working solution prepared in 0.07 M phosphate buffer.

Table 2
Analyses on four separate samples of the same lot of commercial dosage forms

Formulation*	Quantity taken (mg)	Average recovery, % (± S.D., $n = 4$)	Average recovery, % (comparative method, $n = 4$)†	Other declared ingredients
(A) Methimazole tablets, 5 mg	5	97.9 (0.3)	98.3	Lactose, sucrose, talc, magnesium stearate, starch
(B) Cetylpyridinium chloride disinfectant solution, 0.2%	6	98.9 (0.2)	98.2	2-Phenoxyethanol, lignocaine hydrochloride, patent blue V
(C) Benzethonium chloride disinfectant solution, 0.1%	5	103.7 (0.2)	103.5	Acetone, isopropyl acetate, ponceau 4R
(D) Benzalkonium chloride contact lens solution, 0.01%	1	102.4 (1.2)	103.9	Phosphate buffer, disodium edetate
(E) Chlorhexidine gluconate mouth rinse, 0.2%	2	100.1 (0.9)	99.7	Xylitol, sorbitol 70, propylene glycol, ethanol, essential oils
(F) Sodium bromide injections, 25 mg	2.5	101.7 (0.2)	102.3	Valerian extract, sodium glycerophosphate

* Manufactured by: (A) Eli Lilly Italia (Italy); (B) Farmacosmici (Italy); (C) Formenti (Italy); (D) Smith & Nephew (England); (E), (F) Pagni (Italy).

† Methimazole: u.v. spectroscopy; cetylpyridinium and benzethonium: potentiometric titration with potassium ion selective electrode, reference [7]; benzalkonium: two-phase titrimetry, reference [8]; chlorhexidine: gravimetry, reference [9]; bromide: Volhard method.

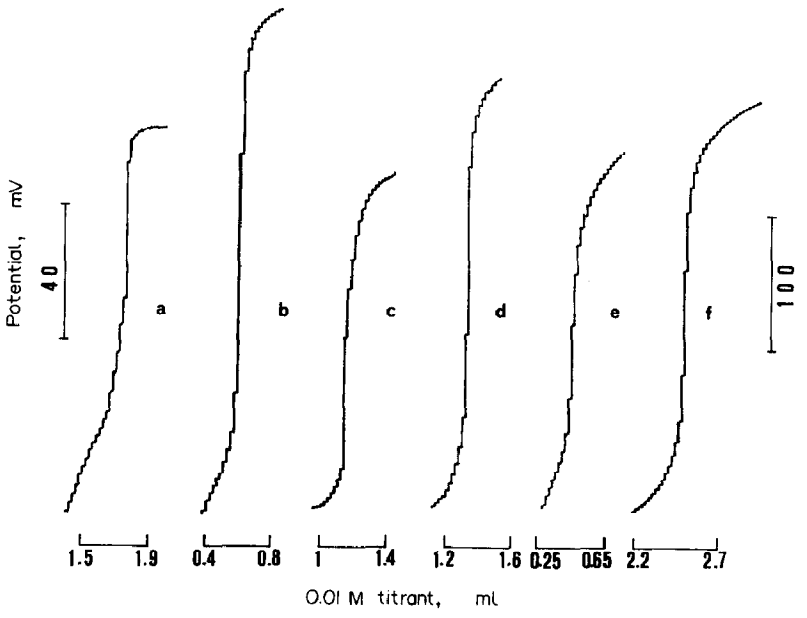

Figure 2
Typical potentiometric titration curves of test solutions containing: a, 4 mg methimazole; b, 2 mg propylthiouracil; c, 4 mg cetylpyridinium chloride; d, 6 mg benzethonium chloride; e, 2 mg chlorhexidine gluconate (commercial mouth rinse); f, 2.5 mg sodium bromide (commercial injections).
The potential scale on the right refers to curve f only.

The response of the silver–silver sulphide electrode to the sulphide level (10^{-1}–10^{-6} M) at strongly alkaline pH was Nernstian, with a slope value of 29 mV per decade at 20°C. In order to prevent sulphide oxidation, ascorbic acid was added to test solutions during these measurements. The indicator electrode behaved reversibly with respect to thiolate, silver and tetraphenylborate ions. It is interesting to note that the response of the electrode to tetraphenylborate at pH 3.4 was linear over the range 10^{-2}–10^{-6} M, with an average slope of 52 mV at 18°C; this allowed the use of the pellet as a good tetraphenylborate sensor. Generally, ions that react with either silver ions or sulphide ions must be regarded as interfering substances. In particular, by taking advantage of the severe interference encountered with mercury(II) ions the pellet electrode can be used for direct mercurimetry, provided that the electrode surface is polished before each titration.

The electrode described was employed for assaying drugs in a wide pH range (about 1–9). In each case the pH value of the test solution was chosen in order to obtain accurate and precise results with an optimum end-point. An acidic medium was used for the analysis of halides, quaternary ammonium compounds and chlorhexidine salts; in this latter case a little Triton X-100 was added to counteract flocculation and the adhesion on the electrode surface of chlorhexidinium tetraphenylborate. On the other hand, neutral or slightly alkaline conditions were necessary for the quantitative determination of the thiolate ions of propylthiouracil or methimazole, which react with mercury(II) to form very slightly soluble sulphides.

The electrode described here, unlike the conventional silver electrode, can be used in solutions containing oxidizing agents. An example of this type of interference is shown in

Fig. 3, where the silver–silver sulphide and the silver electrodes were each used in a silver nitrate titration of a chloride solution containing ferric ions and nitric acid. In this titration the pellet electrode is unaffected by the oxidant, whereas the silver electrode underestimates the end-point by about 20%. A conventional silver sulphide membrane electrode was found to remain unaffected by ferric ions [6]. This could mean that the metallic silver at the surface of the pellet electrode became coated with a film of silver sulphide under the conditions of the above analysis.

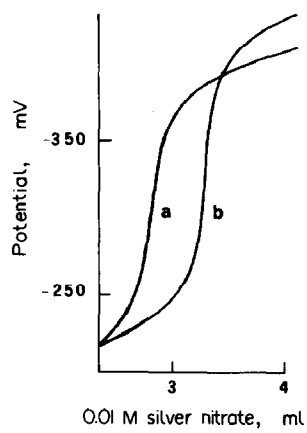

Figure 3
Potentiometric titration curve of a test solution containing 0.6 mmol of nitric acid, 0.036 mmol of sodium chloride and 0.01 mmol of iron(III) nitrate: a, with a conventional silver electrode; b, with the solid-state silver–silver sulphide electrode.

In conclusion, the electrode described in this work represents a convenient alternative for the direct, accurate and precise potentiometric assay of a number of drugs. It also appears to offer some important advantages over the conventional silver wire or silver sulphide membrane electrode. Compared with the latter, the pellet electrode has a very low resistance (0.01 Ω/cm) and is very rugged. Compared with the silver electrode, the pellet electrode is insensitive to certain oxidants and capable of yielding reproducible results without chemical pretreatment.

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