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Short Communication

POTENTIOMETRIC TITRATION OF PHARMACEUTICAL COMPOUNDS IN FORMULATIONS WITH SODIUM TETRAPHENYLBORATE

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Summary. Simple potentiometric titrations are described for the determination of various cationic pharmaceutical compounds with sodium tetraphenylborate; end-points are detected with a tetraphenylborate-selective electrode. Satisfactory results were obtained for the active components in various antihistaminic, neuroleptic, antispasmodic, anticholinergic, tranquilizer and antidepressant preparations. The relative standard deviation at the 25-μmol level is typically 0.3—0.7%.

Ion-selective electrodes have been applied successfully to the determination of various pharmaceutical compounds in drugs [1]. Sodium tetraphenylborate has been extensively used for the determination of univalent cations, including various alkaloids, cationic surfactants, quaternary ammonium compounds and amines, by gravimetric or titrimetric methods. In many titrimetric methods, ion-selective electrodes are used for end-point detection [2—9]. Recently, the construction of a liquid-membrane tetraphenylborate electrode was described, along with its application in the potentiometric titration of various organic cations with tetraphenylborate [10]. Here, this electrode is used in the semi-automatic titration of several pharmaceutical compounds with sodium tetraphenylborate. For most compounds, steep titration curves with large potential breaks were observed. The precision of the titrations was better than 1% in all cases (typically 0.3—0.7%). Application of the method to various commercial pharmaceutical preparations gave satisfactory results.

Experimental

Apparatus. The electrodes, the reaction cell and the titration and recording system were as previously reported [10]. Titrant delivery rates were kept constant at 0.36 ml min^{-1}. Titrations were done at ambient temperature (22 ± 2°C) with constant magnetic stirring.

Reagents. Solutions were prepared with deionized distilled water from reagent-grade materials. The standard 0.010 M sodium tetraphenylborate solution was prepared and standardized as reported previously [10]. Standard solutions of the pharmaceutical compounds were prepared from materials of the highest purity available used as received; generally, 10^{-3} M

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solutions were prepared by dissolving the appropriate amount of the hydrochloride (chlorpromazine, promethazine, imipramine, clomipramine, opipramol, amitriptyline) or bromide (prostigmine, pyridostigmine, clidinium) in water. Thioproperazine bismethane sulfonate was also dissolved in water. Medazepam was dissolved in citrate buffer, pH 2.5. Commercial pharmaceutical preparations were purchased from pharmaceutical industries and local drug stores.

All buffers (0.10 M) were prepared as before [10]. Buffers used were citrate (pH 2.5), acetate (pH 3.3 and 5.0), and phosphate (pH 7.0 and 10.2).

Titration of aqueous solutions of pharmaceutical compounds with standard 0.01000 M sodium tetraphenylborate solution. Pipet into a 50-ml beaker a 25.00-ml aliquot of the sample in the range 2.00×10^{-4}—1.00×10^{-3} M for chlorpromazine hydrochloride, promethazine hydrochloride, imipramine hydrochloride, clomipramine hydrochloride, opipramol dihydrochloride, amitriptyline hydrochloride, thioproperazine bismethane sulfonate, medazepam, clidinium bromide, prostigmine bromide and 4.00×10^{-4}—1.00×10^{-3} M for pyridostigmine bromide. Add 5.00 ml of the appropriate buffer solution, start the stirrer and after the potential has stabilized (ca. 1 min) start the constant-rate burette and the recorder simultaneously to obtain the titration curve. Calculate the amount of the pharmaceutical compound present in the sample titrated in the usual way.

Analysis of pharmaceutical preparations. For tablet preparations, 20 tablets are weighed and powdered. An appropriate weighed amount of the powder (equivalent to about 0.5 mmol of active ingredient) is transferred to a 500-ml beaker, and stirred vigorously with about 400 ml of water for 15 min. The solution is diluted to the mark in a 500-ml volumetric flask and a 25.00-ml aliquot is titrated as described above. For injections, drops and syrups, an appropriate volume of the sample (equivalent to 0.2 mmol of active ingredient) is diluted with water to 200 ml in a volumetric flask and a 25.00-ml aliquot is titrated as described above.

Results and discussion

The optimum pH for each titration, selected to provide accurate precise results, small blanks and steep end-point breaks, was found by titrating each compound at various pH values in the range 2.5—10.2. Titrations at pH < 2.5 are not feasible because the electrode misbehaves in strongly acidic solutions and the sodium tetraphenylborate solution decomposes (cf. [10]). The optimum pH values are listed in Table 1, and the results obtained for the drugs in aqueous solutions and in commercial preparations are shown in Tables 1 and 2, respectively. There is fairly good agreement between the amounts of substance calculated by the titrimetric method with the nominal values. The end-point jumps were steep, except for Anafranil, Noveril and Mestinon tablets, but even in these cases the deviations were acceptable (Table 2). The solutions obtained for titration after dissolution of the commercial preparations were usually turbid, coloured or viscous, because of

TABLE 1

Results obtained for various drugs by potentiometric titration with sodium tetraphenylborate[a]

Compound	Optimum pH	Assay (%)	R.s.d. (%)	End-point break (mV)
Chlorpromazine hydrochloride	3.3	101.5	0.7 (4)[b]	230
Promethazine hydrochloride	3.3	99.0	0.4 (5)	180
Thioproperazine bismethane sulfonate	3.3	98.1	0.6 (6)	180
Imipramine hydrochloride	3.3	101.4	0.7 (4)	250
Clomipramine hydrochloride	3.3	99.9	0.6 (3)	250
Opipramol dihydrochloride	5.0	99.4	0.6 (3)	120
Amitriptyline hydrochloride	3.3	97.9	0.4 (4)	250
Medazepam	2.5	99.7	0.4 (3)	190
Clidinium bromide	3—7	99.7	0.5 (4)	110
Pyridostigmine bromide	3—10	100.2	0.2 (4)	95
Prostigmine bromide	5—10	98.5	0.6 (4)	100

[a]Results are based on the titration of a sample containing about 25.0 μmol of compound. [b]The number in parentheses is the number of determinations.

TABLE 2

Determination of active substances in various pharmaceutical preparations by potentiometric titration with sodium tetraphenylborate

Preparation[a]	Content of drug		R.s.d.[c] (%)
	Nominal	Found[b]	
Chlorpromazine injection (Largactil)	5 mg ml^{-1}	5.1	0.2 (4)
Chlorpromazine tablets (Largactil)	100 mg/tabl.	99.5	0.2 (3)
Promethazine injection (Phenergan)	50 mg/2 ml	50.9	0.4 (4)
Promethazine syrup (Phenergan)	1 mg ml^{-1}	1.03	0.4 (4)
Promethazine tablets (Phenergan)	25 mg/tabl.	25.6	0.4 (4)
Promazine injection (Sparine)	50 mg ml^{-1}	49.6	0.3 (3)
Promazine syrup (Sparine)	10 mg/5 ml	10.3	0.3 (3)
Imipramine injection (Tofranil)	25 mg/2 ml	24.8	0.2 (3)
Imipramine tablets (Tofranil)	25 mg/tabl.	25.4	0.1 (3)
Amitriptyline tablets (Amitriptyline)	25 mg/tabl.	25.9	0.4 (3)
Clomipramine tablets (Anafranil)	25 mg/tabl.	25.3	0.9 (3)
Opipramol tablets (Insidon)	50 mg/tabl.	50.1	0.2 (3)
Trifluoperazine tablets (Stelazine)	5 mg/tabl.	5.2	0.4 (3)
Dibenzepin tablets (Noveril)	240 mg/tabl.	239	0.8 (3)
Cyproheptadine tablets (Periactin)	4 mg/tabl.	4.1	0.9 (3)
Propyromazine[d] drops (Diaspasmyl)	100 mg/10 ml	95.7	0.7 (3)
Prostigmine[d] tablets (Prostigmine)	15 mg/tabl.	15.0	0.3 (4)
Pyridostigmine[d] tablets (Mestinon)	60 mg/tabl.	62.7	0.2 (3)

[a]Compound is present as the hydrochloride, except where indicated. [b]Compounds titrated at optimum pH (Table 1) or at pH 3.3 for compounds not included in Table 1. End-point breaks were as listed in Table 1; for unlisted drugs, the breaks were 160—250 mV, except for dibenzepin (125 mV). [c]Number of determinations in parentheses. [d]Present as hydrobromide.

the excipients present. All these solutions could be titrated potentiometrically without difficulty.

Chlorpromazine has been titrated potentiometrically with silver nitrate and a chloride or silver ion-selective electrode, after combustion of the sample to release chloride [2], which is time-consuming. Selig [4] titrated chlorpromazine and other pharmaceutical substances with sodium tetraphenylborate and a fluoroborate ion-selective electrode. The substances listed in Tables 1 and 2 have not previously been determined by potentiometric titrations with sodium tetraphenylborate to a tetraphenylborate-selective electrode end-point.

The proposed procedures are simple, accurate and sensitive and are suitable for quality control. Their main limitation is lack of selectivity, as any ion that precipitates tetraphenylborate at the relevant pH will cause positive errors. Fortunately, many pharmaceutical preparations contain the active ingredient in mixtures with inert excipients.

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