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Phosphorus-doped and undoped glassy carbon indicator electrodes in controlled-current potentiometric titrations of bromide- or chloride-containing active ingredients in some pharmaceutical preparations

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Abstract

Phosphorus-doped glassy carbon (as a novel material) and glassy carbon (Sigri commercial sample) were applied as potentiometric indicator electrodes in the titrimetric determination of active components with bromide or chloride in their molecules in different pharmaceutical preparations (Buscopan, Prostigmine, Isoptin, Bedoxin, Akineton and Trodon). After the necessary pre-treatment of the electrode surfaces and sample dissolution, the halide was titrated with a standard solution of silver nitrate (indirect determination). Amounts of 10–20 μmol of the investigated active ingredients per titration were determined with a relative standard deviation that, depending on the nature of indicator electrode, determined molecules and filler components, was in the range of 0.3–2.7%. The results obtained were compared with those of the official methods and with those obtained by potentiometric titrations using silver electrode. The titrimetric procedures developed are relatively fast, easy, economical and can be used to analyse of a large number of pharmaceutical products.

Keywords: Phosphorus-doped glassy carbon electrode; Potentiometric titration; Bromide- or chloride-containing pharmaceutical preparations

1. Introduction

Some active ingredients in drug formulations are in the form of bromide salts of weak organic bases, and more often as their hydrochlorides. The development of suitable methods for their analysis has been a subject of active interest. Some of the active ingredients that are nowadays frequently used, and which have been subject of this study are: hyoscine butylbromide ($C_{21}H_{30}BrNO_4$), neostigmine bromide ($C_{12}H_{19}BrN_2O_2$), biperiden hydrochloride ($C_{21}H_{30}ClNO$), pyridoxine hydrochloride ($C_8H_{12}ClNO_3$), tramadol hydrochloride ($C_{16}H_{26}ClNO_2$) and verapamil hydrochloride ($C_{27}H_{39}ClN_2O_4$). Their analysis, both as pure substances and pharmaceutical preparations of various formulations have been carried out by different methods, ranging from direct potentiometry with membrane ion selective electrodes [1–5], titrations [4–9], voltammetric techniques [10,11] through ultraviolet/visible spectrophotometry [12–17], atomic emission spectrometry [18], to chromatography [19–23]. However, the majority of these procedures are either time consuming or require highly specialized, expensive, and sophisticated instrumentation. As far as official methods are concerned, previous edition of Farmakopeja SFRJ [24], as well as the US Pharmacopeia [25] and British Pharmacopoeia [26] (if they contain at all the corresponding monographs), recommend for the determination of pure active substance non-aqueous titration, whereas for their determination in different formulation recommend, after the appropriate sample pre-treatment, titrimetry [24,26] or spectrophotometry [24–26]. New editions of European Pharmacopoeia [27] and Jugoslovenska farmakopeja

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(Ph. Jug. V) [28] replace the non-aqueous titration in some cases for the assay of bromide salts in pure substance with argentometric titration with potentiometric end-point determination, whereas for the determination of chloride salts they introduce alkalimetry in alcohol–water mixture with potentiometric end-point detection. Thus, the intention was to replace the non-aqueous titration with a method requiring the use of aqueous reagents, which are less hazardous and more environment-friendly. However, this method could not be successfully applied in a number of cases of chloride determination [29].

In view of the fact that controlled-current potentiometric titrations with phosphorus-doped glassy carbon and Sigri glassy carbon indicator electrodes have been successfully applied for the determination of halides in model solutions [30–32], continuing on our previous study of argentometric determination of bromine-containing active ingredients in some drug formulations [6], the subject of this work was to investigate the possibility of application the above electrodes for the determination of bromide and chloride in some pharmaceutical preparation. Besides, a potentiometric titration procedure was applied, using a silver wire as indicator electrode.

2. Experimental

2.1. Reagents and samples

All chemicals used were of analytical reagent grade. Aqueous solutions were prepared with doubly distilled water.

Contents of bromide were determined in the following pharmaceutical preparations: hyoscine butylbromide was analyzed in Buscopan dragées (Zdravlje, Leskovac, Serbia and Montenegro) and injections (Boehringer, Ingelheim, Greece), and neostigmine bromide in Prostigmine tablets (Roche, Basle, Switzerland).

Contents of chloride were determined in the following pharmaceutical preparations: verapamil hydrochloride in Isoptin dragées (Lek, Ljubljana, Slovenia), pyridoxine hydrochloride in Bedoxin tablets (Galenika, Belgrade, Serbia and Montenegro), biperiden hydrochloride in Akineton tablets (Lek, Ljubljana, Slovenia) and tramadol hydrochloride in Trodon capsules (Hemofarm, Vršac, Serbia and Montenegro).

Zdravlje (hyoscine butylbromide) and Roche (neostigmine bromide) are thanked for supplying the pure active substances.

Standard silver nitrate solution, 1×10^{-2} M, was prepared by dissolving the necessary amount of solid salt in double distilled water. The prepared solution was stored in a dark flask and standardized against sodium chloride solution, 1×10^{-3} M, using all three titration methods. Sodium chloride was previously heated at 500 °C.

2.2. Apparatus

The course of indirect controlled-current potentiometric titration was monitored using the glassy carbon (GC) electrode doped with 1.0% of phosphorus (w/w in the starting resin, P-GC10) and a standard GC electrode (Sigri Electrographit, carbonized at 2400 °C, Sigri-GC). Both GC electrodes were in the form of rods (Ø 3 mm) and were mounted in Teflon holders. The P-GC10 was prepared by carbonizing a phenol-formaldehyde resin with doping element ($(NH_4)_2HPO_4$) at 1000 °C [31].

The microcomputer-aided [33] potentiometric ($I = 1\ \mu A$) titrations were carried out with a negatively polarized indicator electrode coupled to a Radiometer saturated calomel electrode (SCE) via a double-junction salt bridge ([GC(−)|SCE(+)]) [30–32]. In all experiments, only the electrode disc area was exposed to the solution. Comparative argentometric potentiometric titrations were performed with the aid of a silver wire electrode connected via a suitable SCE, and the appropriate resistor, to ensure a zero-current regime.

The titrant was added continuously by a Radiometer ABU 80 automatic piston burette at an optimum rate of 0.25 $cm^3\ min^{-1}$.

The comparative spectrophotometric measurement were carried out on an Anthelia Data Spectrophotometer, (SECOMAM, France).

The Shimadzu Class LC-10 chromatographic system with UV/VIS, SPD-10A detector at 272 nm was used according to the manufacturer's procedure.

2.3. Recommended procedure

2.3.1. Sample preparation for indirect titrations

Pure active substance. Accurately weighed amounts of about 100–200 μmol were dissolved in water and quantitatively transferred into a 100 cm^3 calibrated flask. After diluting to volume with the same solvent, 10 cm^3 aliquots were taken for the analysis.

Dragées, tablets, capsules. A known number of dragées or tablets, and the quantitative content of capsules were ground to a fine powder. An accurately weighed portion of the powder containing about 100–200 μmol of active compound was dissolved in water, diluted to volume in a 100 cm^3 calibrated flask and 10 cm^3 aliquots were taken for the analysis. Measurements were performed without sample filtration.

2.3.2. Electrode pre-treatment

The GC electrodes were polished with alumina powder (Buehler LTD, micropolish, Linde A, 0.3 and 0.5 μm α-alumina) wetted with double distilled water, to attain a mirror finish (about 5 min) before each titration. Afterwards, the electrode was washed in an ultrasonic bath with double distilled water to remove any residual polish. Then it was negatively polarized at 1 V against SCE in a diluted solution

of potassium nitrate (1×10^{-5} M) until the residual current dropped to 5 μA.

The silver wire electrode was polished and washed with distilled water before each titration.

2.3.3. Measurements

Controlled-current potentiometric titrations. The aliquot was diluted with 5 cm^3 of water and the mixture was titrated with standard silver nitrate solution. The indicator electrode was P-GC10 or Sigri-GC. The titration end-point was determined using the mentioned computer program [33] for finding maximum on the first derivative of titration curves in bromide determination, or the intersection of the straight lines before and after the equivalence point in chloride determination.

Potentiometric titrations. The procedure was the same in zero-current regime with silver indicator electrode. The titration end-point was determined using the mentioned computer program [33] for finding maximum of the first derivative of titration curves.

In all cases results were corrected for the blank (10^{-5} M solution of potassium nitrate) except for the potentiometric determination of bromide using Ag wire.

2.3.4. Comparative methods

The procedure for comparative methods have been described in the Farmakopeja SFRJ [24] or the US Pharmacopeia [25] or were recommended by the manufacturer.

Content of biperiden in Akineton tablets was determined spectrophotometrically using bromophenol blue (BPB) [13].

3. Results and discussion

3.1. Indirect determination of the active component with bromide

In the case of the indirect determination of neostigmine bromide in pure substance and in Prostigmine tablets the shapes of titration curves obtained with [P-GC10(−)|SCE(+)], ($I = 1$ μA) method were well defined (Fig. 1, curves 4 and 5). As can be seen, the controlled-current potentiometric titration with P-GC10 indicator electrode compared favourably with the potentiometric titration performed with the aid of an Ag wire (Fig. 1, curves 2 and 3), because the change of the potential around the equivalence point obtained with P-GC10 is about three times greater than that obtained using a silver electrode. By comparing the behaviour of the Sigri-GC with that of the P-GC10 electrode it can be noticed that the total change of the potential was similar with both of them, as could be expected on the basis of titration curves of bromide in the model solution [30–32].

The differences in the electrode potential before the equivalence point can be explained by the nature of potential-forming reaction [31]. In the case of Ag it is mainly the reaction with the halide involved, while at P-GC10 electrode it may be also the reduction of H^+ or H_2O, depending on the electrolyte composition. After the equivalence point the electrode potential is determined by silver ions. Because of this, the electrode potential and the shape of the titration curve after the equivalence point are very similar to those obtained with the Ag electrode. It can also be noticed that the maximum of the curves (Fig. 2) obtained with the silver electrode (curves 2 and 3), corresponding to the titration end-point, coincides with the first derivative maximum of the curves obtained with P-GC10 (curves 4 and 5), corrected for the blank (curve 1). The same also holds for the Sigri-GC. As can be seen from Table 1, the results of argentometric titration show a satisfactory agreement in respect of accuracy and precision.

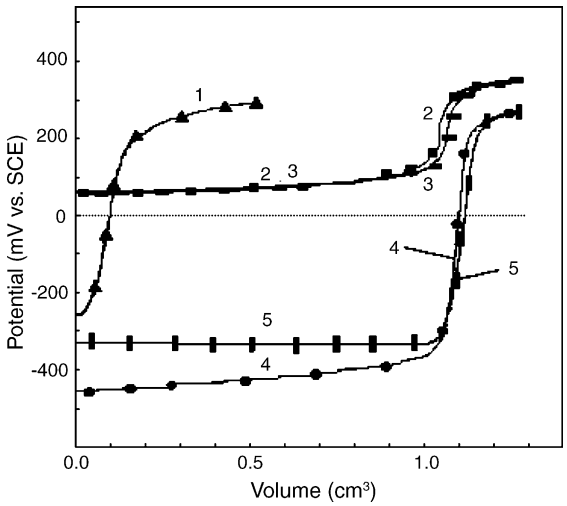

Fig. 1. Potentiometric titration curves of the blank (1) and 3.0 mg of neostigmine bromide in Prostigmine tablets (2, 4) and pure substance (3, 5) with 1×10^{-2} M $AgNO_3$: 1, 4, 5) [P-GC10(−)|SCE(+)], ($I = 1$ μA); 2, 3) [Ag|SCE], ($I = 0$).

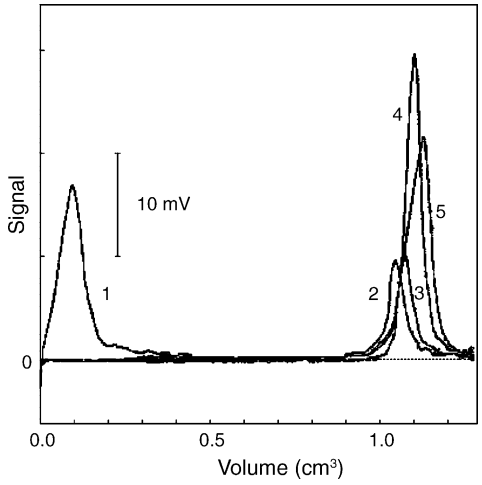

Fig. 2. Derivative potentiometric titration curves of the blank (1) and 3.0 mg of neostigmine bromide in Prostigmine tablets (2, 4) and pure substance (3, 5) with 1×10^{-2} M $AgNO_3$: 1, 4, 5) [P-GC10(−)|SCE(+)], ($I = 1$ μA); 2, 3) [Ag|SCE], ($I = 0$).

Table 1
Results of determination of some bromide-containing active ingredients in drug substances and chosen pharmaceutical preparations ($n = 6$)

Compound	Method of determination							
	Potentiometric [P-GC10(−)|SCE(+)] ($I = 1\ \mu A$) titration		Potentiometric [SigriGC(−)|SCE(+)] ($I = 1\ \mu A$) titration		Potentiometric [Ag|SCE] titration		Official method	
	Found (mg)	RSD (%)	Found (mg)	RSD (%)	Found (mg)	RSD (%)	Found (mg)	RSD (%)
Hyoscine butylbromide								
Pure substance (99.9%)	99.1%	0.6	100.1%	0.4	100.4%	0.4	99.7%[a]	0.5
Buscopan dragées (10 mg)	9.80	0.3	10.1	2.7	10.00	0.7	10.9[b]	4.0
Neostigmine bromide								
Pure substance (99%)	100.5%	0.6	99.9%	0.4	98.4%	0.0	99.1%[a]	0.3
Prostigmine tablets (15 mg)	15.20	0.6	15.31	0.5	15.3	1.4	15.7[c]	3.2

n: number of measurements.
[a] Non-aqueous titration [24].
[b] Spectrophotometric determination according to the manufacturer.
[c] Spectrophotometric determination [25].

Typical titration curves of hyoscine butylbromide are presented in Fig. 3. As can be seen, in the case of indirect titration applying the P-GC10 indicator electrode (curves 3 and 4) another potential jump appears before the equivalence point, so that the potential jump around the equivalence point is lower. Hence, the curve shape after the first potential jump is similar to that obtained with silver electrode (Fig. 3, curves 1 and 2). The appearance of two potential jumps for the investigated drug formulation and pure substance is probably a consequence of the nature of titrand. Namely, the presence of hyoscine butylbromide yielded fast adsorption of the precipitate on the P-GC10 surface, which made the electrode behave as if it were a silver one. The difference in the potential of Ag electrode (curves 1 and 2) and that of the P-GC10 measured after the first potential jump (curves 3 and 4) is probably a consequence of the fact that the curves 1 and 2 were obtained at $I = 0\ \mu A$, whereas the curves 3 and 4 were obtained at $I = 1\ \mu A$. Similar curves were also obtained by applying the Sigri-GC electrode. The end-point determination in this situation was possible from the second well-defined maximum, with the correction for the blank. The obtained results were in good agreement with potentiometry with Ag electrode (Table 1).

By the indirect titration of hyoscine butylbromide in injections, due to the presence of an excess of chloride, the second potential jump of bromide cannot be registered because of the beginning of the titration of chloride. If however, hyoscine butylbromide was determined on the basis of the first jump, significantly lower results (about 15%) were obtained, as could expected. Because of that the indirect determination of hyoscine butylbromide in injections was not possible.

The developed procedures were also used to determine bromide in the above preparations present as synthesis impurities. For this reason, the results obtained by applying the controlled-current potentiometric titrations (indirect determination) were compared with those of the official or the manu-

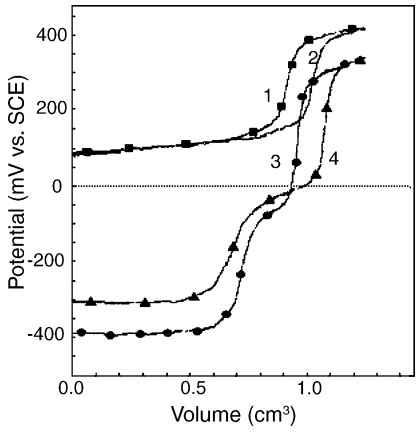

Fig. 3. Potentiometric titration curves of hyoscine butylbromide obtained in pure substance (2, 4), and Buscopan dragées (1, 3) with 1×10^{-2} M $AgNO_3$: 1, 2) [Ag|SCE], ($I = 0$) and 3, 4) [P-GC10(−)|SCE(+)], ($I = 1\ \mu A$). Content of active ingredient (mg): (1, 3) 4.03; (2, 4) 4.44.

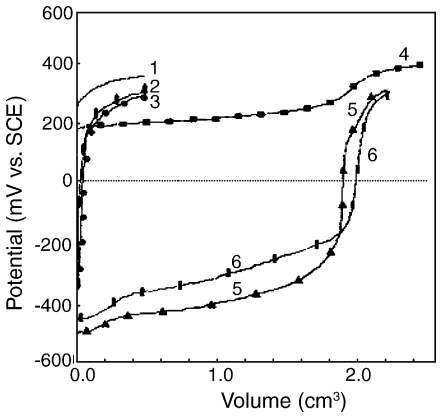

Fig. 4. Potentiometric titration curves of the blank (1–3) and 9.60 mg of verapamil hydrochloride in Isoptin dragées (4–6) with 1×10^{-2} M $AgNO_3$: (1, 4) [Ag|SCE], ($I = 0$); (3, 5) [Sigri-GC(−)|SCE(+)], ($I = 1\ \mu A$); (C2, 6) [P-GC10(−)|SCE(+)], ($I = 1\ \mu A$).

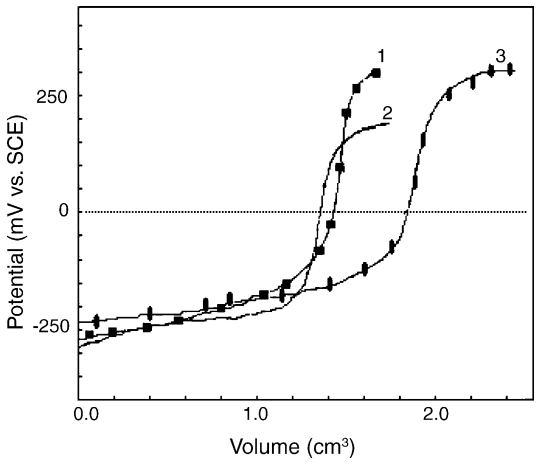

Fig. 5. Potentiometric [P-GC10(−)|SCE(+)], ($I = 1\ \mu A$) titration curves of 4.65 mg tramadol hydrochloride in Trodon capsules (1); 4.40 mg biperiden hydrochloride in Akineton tablets (2); 4.00 mg pyridoxine hydrochloride in Bedoxin tablets (3). Titrant: 1×10^{-2} M $AgNO_3$.

facturers' methods based on the determination of their active organic components (direct determination).

As was observed in our previous work [6], the official method from Farmakopeja SFRJ [24] for the determination of active compound in Prostigmine tablets was disadvantageous comparing with the method from the US Pharmacopeia [25] because the obtained result was about 30% lower than the declared content, while the spectrophotometric method gave similar results (Table 1). In the case of the determination of hyoscine butylbromide in Buscopan dragées the spectrophotometric method described in the British Pharmacopoeia [26] did not give satisfactory results. For these reasons, a modified procedure (manufacturer's procedure) was applied. The modification consisted in the extraction of the active component with the aqueous 0.1 M hydrochloric acid, which produced results that were closer to the declared content (Table 1).

As can be seen from Table 1, a better precision is obtained in almost all cases of the determination of pure substance. Also, the results obtained using both GC electrodes and Ag wire electrode are mainly in good agreement with the declared contents. The higher relative error, as well as the lower precision of the determination of active component in the commercial product by the comparative spectrophotometric method can be ascribed to the extraction operation involved in this procedure, which is not the case in the three indirect procedures of potentiometric titration.

3.2. Indirect determination of the active component with chloride

The advantage of the P-GC10 and Sigri-GC electrodes over Ag wire was even more pronounced in the case of the titration of chloride. Namely, the shape of the potentiometric titration curves were clearly defined in all the cases of the investigated preparations (Figs. 4 and 5), and the potential change around the equivalence point was four times higher than the change obtained using Ag wire.

In this case the titration end-point was determined on the basis of the intersection of the straight lines on the titration curve before and after the equivalence point. This yielded the more accurate results than in the case of end-point determination from the maximum of the first derivative. Namely, the electrode potential measured in the saturated solution of silver chloride was close to the value corresponding to the potential rise on the titration curve. It was also necessary to take into account the blank titrations.

The certain advantage of using the P-GC10 electrode compared with the Sigri-GC as indicator electrode was due to the difference in adsorption properties of chloride and the nature of GC surfaces. Namely, depending on the analysed preparation, silver chloride usually adsorbed on the Sigri-GC surface. This resulted in the different reproducibility of the shape of titration curves obtained with different GC electrodes.

Direct determination of biperiden hydrochloride in Akineton tablets was carried out by spectrophotometric method with bromphenol blue as colourant [13], because the pharmacopeas [24–28] did not contain the corresponding monograph, and no manufacturer's procedure was available. However, the application of the mentioned procedure yielded the results that were significantly lower (by about 10%) than the declared content.

The results of chloride determination are given in Table 2. As can been seen, the results obtained by the official methods are comparable with those of argentometric titration, except for the determination of verapamil hydrochloride in Isoptin dragées, where the results obtained by official method were significantly lower, which was probably a consequence of the losses due to the extraction process.

Table 2
Results of determination of active component with hydrochloride in chosen pharmaceuticals preparations ($n = 6$)

Pharmaceutical preparation	Method of determination											
	Potentiometric [P-GC10(−)|SCE(+)] ($I = 1\ \mu A$) titration			Potentiometric [SigriGC(−)|SCE(+)] ($I = 1\ \mu A$) titration			Potentiometric [Ag|SCE] titration			Official method		
	n	Found (mg)	RSD (%)	n	Found (mg)	RSD (%)	n	Found (mg)	RSD (%)	n	Found (mg)	RSD (%)
Akineton tablets[a]	6	2.08	1.3	6	2.19	0.6	6	2.20	0.5	–	–	–
Trodon capsules[b]	6	49.1	0.8	6	48.6	2.7	6	49.3	1.3	6	49.0[c]	0.5
Bedoxin tablets[d]	6	19.3	0.6	6	19.6	1.1	6	19.7	0.4	3	19.8[e]	0.5
Isoptin dragées[f]	6	78.5	0.9	6	78.8	2.1	6	79.6	0.2	3	74.9[e]	0.8

n: number of measurements.
[a] 2 mg biperiden hydrochloride per tablet.
[b] 50 mg tramadol hydrochloride per capsule.
[c] HPLC determination according to the manufacturer.
[d] 20 mg pyridoxine hydrochloride per tablet.
[e] Non-aqueous titration [24].
[f] 80 mg verapamil hydrochloride per dragée.

4. Conclusion

The controlled-current potentiometric titrations with GC indicator electrodes applied to the indirect determination of the active components of bromide- or chloride-containing preparations are mainly comparable in respect to their accuracy, whereas in respect of precision the P-GC10 has a certain advantage. It may be due to the adsorption the fact of silver chloride on the Sigri-GC surface. Still, the both GC electrodes appeared to be more suitable than silver indicator electrode, especially in the chloride determination because the potential change around the equivalence point was greater.

If controlled-current potentiometric titrations were compared with the official methods for the determination of the pure active substance with bromide [27,28], there are no substantial differences between them either in respect of sample preparation, or accuracy and precision. However, our methods were advantageous as the required amounts of sample was above 75 times smaller. Besides, in the case of determination of neostigmine bromide in pure substance the non-aqueous titration has been replaced with argentometric titration, which is less hazardous and more environment-friendly. In addition, in the analysis of particular pharmaceutical preparations, our methods appear to be superior because they do not require any special preparation of the sample, whereas in almost all instance, the official methods include extraction and filtration before measurement. Therefore, the proposed methods are faster, easier and often give a higher precision of determination (Tables 1 and 2). The titrimetric procedures developed are simple, economical, and can be used to analyse a large number of pharmaceutical products.

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