

Bromide Determination in Pharmaceutical Preparations Using Indirect Gas-Diffusion Flow Injection Method with Amperometric Detector

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Abstract

The indirect gas-diffusion flow injection method (FI) was modified, optimized and successfully applied to bromide determination in various samples such as active substances, drugs, organic substances and water samples. The method is based on the oxidation of bromide to bromine in acidic medium, which diffuses through PTFE membrane into the acceptor flow that carried bromine to the amperometric cell. The flow amperometric detection was carried out at the potential of +0.65 V (vs Ag/AgCl) when injected sample volume was 100 μ L. Results obtained by FIA were confirmed by cyclic voltammetry (CV). The linear calibration graph was obtained over the concentration range 0.1–10 $\times 10^{-3}$ mol/L and 2.5–100 $\times 10^{-6}$ mol/L bromide solutions. Relative standard deviation was 1.23% for 5 $\times 10^{-6}$ mol/L bromide solution and 0.11% for 0.25 $\times 10^{-3}$ mol/L bromide solution ($n=6$, for both cases). The limit of detection was 5 $\times 10^{-8}$ mol/L. The described method requires small quantities of samples and prior extraction of the analytes is not necessary. The method enables 60 analyses per hour.

Keywords: bromide, gas-diffusion, amperometric detection, pharmaceutical active substances, drugs

Introduction

Having in mind the importance of bromide determination in various fields, chemical and pharmaceutical industry, quality control of water etc., it is not a surprise that many FIA methods were developed for bromide determination. The following as detectors were used: spectrophotometry [1, 2], chemiluminescence [3] and potentiometry [4] with bromide-selective electrodes [5, 6]. Van Staden determined iodide, chloride and bromide by combining FIA potentiometry with an ion exchange column [7]. Bromide in the mixture with other anions was determined by ion chromatography [8], amperometrically and potentiometrically after separation by ion chromatography [9]. Some papers

describe the application of flow injection for determination of different analytes in pharmaceutical products [10-12].

According to U.S. Food and Drugs Administration (FDA) data, 2% of pharmaceutical preparations are in hydrobromide form and 5% are in bromide salt form. These preparations are mainly used as bronchodilators and miorelaxants. One of the active substances for bronchodilators is fenoterol hydrobromide ([1-(3,4-dihydrophenyl)-2-(4-hydroxy- α -methylphenylethylamino)ethanol]hydrobromide) (FHBr). For bromide determination in biological samples (plasma and urine) and pharmaceutical preparations different techniques were applied, HPLC [13, 14], gas chromatography combined with mass detection (GC-MS) [15-17], voltammetry [18], spectrophotometry [19] and sequential injection analysis (SIA) [20]. HPLC techniques were applied to determine pancuronium bromide in miorelaxant "Pavulon" [21] and for separation of ipratropium bromide (IPB) and similar products [22].

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According to European Pharmacopoeia [23], fenoterol hydrobromide was determined volumetrically, in pharmaceutical preparations, pancuronium bromide potentiometrically in non-aquatic media [24], and ipratropium bromide purity was determined potentiometrically with silver nitrate in non-aquatic media [24].

In this paper bromide determination was based on its oxidation to bromine that diffuses through PTFE membrane into the sulphuric acid acceptor flow in gas-diffusion unit. Acceptor flow brings bromine to an amperometrical detector. Potassium-permanganate (containing sodium chloride) and potassium bromate were used as oxidizing reagents. FIA experiments were confirmed by cyclic voltammetry, which was also used for the explanation of the kinetics and mechanism of electrode processes.

The developed method was applied to determine bromide in various samples: water, pharmaceutical preparations and organic substances. Simple sample preparation was the advantage in comparison with other methods described in the literature. Through the determination of bromide it was possible to determine the purity of active substances and their quantities in drugs.

Experimental Procedures

Reagents and Chemicals

Reagents used for these experiments were of analytical grade and made with deionized water that was filtrated and degassed. Sulphuric acid, potassium bromate, sodium chloride, and potassium bromide were made with reagents of analytical grade purity (Merck). Potassium permanganate solution was prepared by diluting stock solution and removing excess of MnO_2 by filtration. Potassium bromide concentration was determined volumetrically [25].

Instrumentation and Apparatus

The FIA apparatus scheme is presented in Figure 1. Peristaltic pumps were employed to provide constant flows (P). Injection valve (I), model 5020 (Rheodyn, Cotati, USA) was equipped with a sample loop, 100 μ L and 200 μ L volume. Flow amperometrical detector (FC), model LC-17A (BAS, West Lafayette, USA), consisted of paired round platinum electrodes (working electrode), Ag/AgCl reference electrode (in 3 mol/L NaCl), model RE-4 (BAS, Lafayette, USA) and auxiliary electrode. Teflon gasket determined the sample volume inside flow detector (by changing its thickness, 0.05 or 0.1 mm) and also separated auxiliary and working electrodes. Working electrode potential was set and controlled by potentiostat (PO), model MA 5450 (Iskra, Kranj, Slovenia). Potentiostat was also used for measuring the current. FIA signals were recorded by the recorder (RE), model 61 Servograph (Radiometer, Copenhagen, Denmark). A "Chemifold type II" unit was used for mixing reagents and samples. All

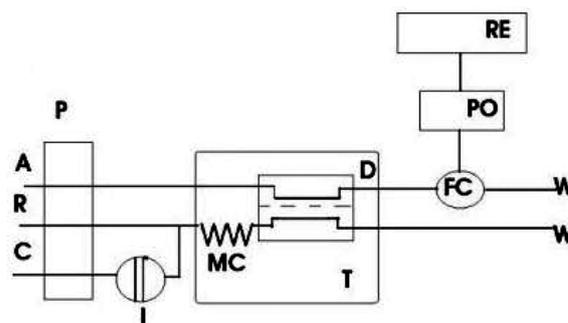


Fig. 1 Schematic presentation of the FIA apparatus used for amperometric determination of bromide content. A – acceptor solution; R – reagent; C – carrier; P – peristaltic pumps; I – injection valve; MC – mixing coil; D – gas-diffusion unit; FC – flow electrochemical cell; PO – potentiostat; RE – writer; T – thermostat; W – waste.

tubes were made of Teflon, 0.5 mm i.d. Gas-diffusion unit was made after model Shenyang Film Projector Factory (Shenyang, China). Temperature was regulated by thermostat, type VEB MLW, Germany.

Cyclic voltammetric experiments were registered on a Metrohm 797 VA Computance instrument (Herisau, Switzerland). Triple electrode system consisted of: working electrode, rotating platinum disk (RDE); reference electrode Ag/AgCl in potassium chloride (3 mol/L) and auxiliary platinum electrode. The PC software provided controls for the measurement, recording the measuring data and evaluating it.

Procedure Applied for Bromide Determination

Indirect bromide determination was based on a combination of gas-diffusion FIA method with amperometric detection. Injected bromide solution, taken by carrier, sulphuric acid solution (C), entered into the mixing coil (MC) where it was mixed with oxidizing reagent (R). In acidic media bromide was oxidized to bromine, then it enters donor flow and gets into a gas-diffusion unit, where it diffuses through PTFE membrane into acceptor flow, sulphuric acid solution (A). Other reaction products left the system as waste (W). Bromine entered into amperometrical flow through cell (FC) and it was reduced to bromide on platinum electrode. The recorder (RE) registered the current whose strength was proportional to bromide concentration in standard and/or sample.

Discussion and Results

Optimisation of FIA Method for Bromide Determination

The method was optimized with two different oxidizing agents (potassium permanganate and potassium bro-

mate). The effect of applied potential was investigated in the potential range +0.25 to +0.90V versus Ag/AgCl reference electrode. Hydrodynamic voltammogram of standard bromide solution (2.5 mmol/L in 2 mol/L sulphuric acid) indicated that high values suitable for measurements were obtained between +0.40 and +0.75V. For further experiments +0.65V was used and cyclic voltametry confirmed the chosen potential.

Sulphuric acid concentration as a carrier was investigated by triple injection of standard bromide solution (2.5 mmol/L) while varying sulphuric acid concentration from 1.0 to 5.0 mol/L. When potassium permanganate was used as oxidizing agent a dependence of FIA peak height with sulphuric acid concentration was described by the equation

$$I = 12.303 + 0.4667 e^{c/1.582}$$

where I was the current in μA , and c was the concentration of acid in mol/L ($r^2=0.9925$). FIA peak height exponentially increased with the concentration of acid. In further work 2mol/L sulphuric acid was used as a carrier. When potassium bromate was used as oxidizing agent, the exponential dependence was also obtained but it decreased with the concentration of acid. It was described with the equation

$$I = 27.407 - 2.8167 e^{c/1.914}$$

where I was the current in μA , and c was the concentration of acid in mol/L ($r^2=0.9908$).

For further work 1mol/L sulphuric acid was used as the highest signals were obtained.

By injecting the standard bromide solution (1.00 mmol/L in 2mol/L sulphuric acid) the linear dependence was obtained with the increase of temperature from 20 (to 60°C. It was described by the equation:

$$I = (0.5775 \pm 0.0367)t - (8.33 \pm 1.56)$$

where I was the current in μA and t the temperature in °C. The correlation coefficient was 0.9940.

Temperature variation does not affect only the reaction rate, but also the solubility of bromine, diffusion process and bromine reduction on platinum working electrode. Since the method is sensitive enough at room temperature, all further experiments were done under the same conditions.

Effect of acceptor (0.01 mol/L sulphuric acid) flow rate and direction was investigated at constant donor flow rate (3.0 mL/min). When using permanganate as the reagent the highest signals were obtained when acceptor flow rate was 1.6 mL/min. The highest signal was obtained at 1.2 mL/min flow rate when bromate was used. Switching between donor and acceptor flow direction (parallel and opposite) did not make significant signal height difference; therefore all further experiments were done with parallel acceptor and donor flows.

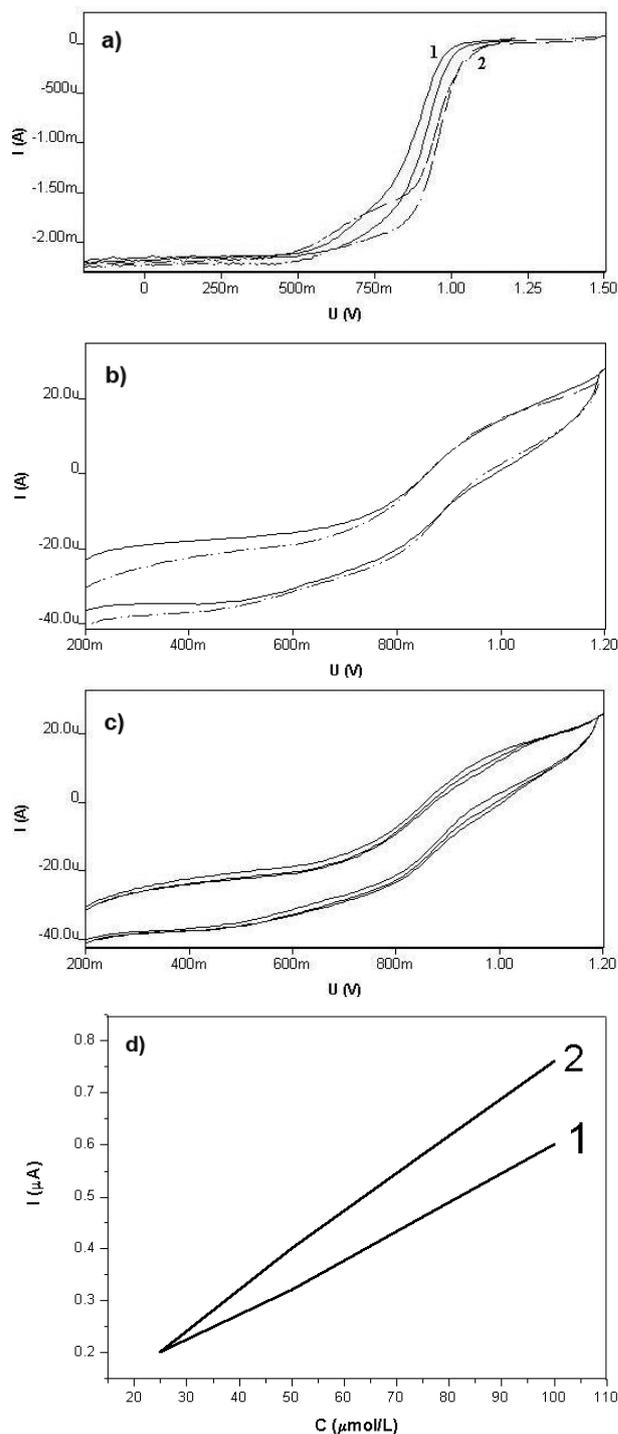


Fig. 2 Cyclic voltammograms obtained at 1mm Pt electrode at $v = 50$ mV/s.

a) cyclic voltammograms of 0.05 mol/L KMnO_4 i 1.0 mmol/L KBr solutions in 2 mol/L sulphuric acid (1); 0.05 mol/L KMnO_4 with 0.04 mol/L NaCl and 1.0 mmol/L KBr in 2 mol/L sulphuric acid (2); b) cyclic voltammograms of 0.05 mol/L KBrO_3 and 1.0 mmol/L KBr solutions in 1 mol/L sulphuric acid and 0.05 mol/L KBrO_3 with 0.04 mol/L NaCl and 1 mmol/L KBr in 1 mol/L sulphuric acid; c) cyclic voltammograms of 0.05 mol/L KBrO_3 and (0.1 mmol/L KBr:NaCl in ratios 1:500; 1:1000; 1:10000) in 1 mol/L sulphuric acid; d) calibration runs when KMnO_4 (1) was used as oxidation reagent and when KBrO_3 was used (2).

If 0.05 mol/L potassium permanganate solution with 0.04 mol/L NaCl was used as an oxidizing reagent instead of pure 0.05 mol/L permanganate, better sensitivity was obtained, which could be noticed on cyclic voltammograms. This could be explained by homogeneous catalysis that was caused by chloride (Fig. 2a, curve 1 and 2). However, there was no difference in signal height if NaCl solution was added to bromate standard solution, which was also confirmed by cyclic voltammetry (Fig. 2b). Besides better sensitivity, the presence of chloride in permanganate solution enabled bromide determination in samples that contained chloride in concentrations up to 1000 times higher than bromide [26]. However, when pure bromate was used there was no interference from chloride present in bromide samples. There was no signal height difference higher than $\pm 1\%$ when bromide samples contained chloride in ratios 1:500, 1:1,000 and 1:10,000 (Fig. 2c).

During optimization of modified procedure for bromide determination, the influence of Teflon gasket thickness was also investigated. Its thickness effects both the working solution volume and the bromine concentration at platinum working electrode. The highest FIA signals were obtained when we used the thinnest gasket (0.05 mm). However, for routine analyses, when bromide concentration was above quantification limit and when it was more important to work in wider linear range, the use of 0.10 mm gasket enabled satisfactory sensitivity.

Comparison of sensitivities achieved by different oxidizing reagents, based on obtained calibration curves, was presented in Fig. 2d.

Since better sensitivity was obtained when bromate was used as the agent (expressed as curve slope) this reagent was used in further experiments.

Effect of Interferants on Applied FIA System

High sensitivity for bromide determination was caused by the fact that PTFE membrane used in gas-diffusion unit was a barrier for many ionic species that could interfere the determination. However, a few anions were tested as possible interferants. Amperometric detector response did not differ from the base line when the following solutions were injected: 0.01 mol/L thiocyanate, 0.1 mol/L acetate, 0.1 mol/L fluoride, 0.1 mol/L nitrate and 0.001 mol/L iodate.

Under experimentally defined conditions two linear ranges were obtained: $2.5\text{--}100.0 \times 10^{-6}$ mol/L ($I = (0.0917 \pm 0.000403)c + (0.0179 \pm 0.02258)$, ($r = 0.9962$)) and $0.1\text{--}10 \times 10^{-3}$ mol/L ($I = (3.7928 \pm 0.0916)c + (0.4674 \pm 0.2236)$ ($r = 0.9999$)). Relative standard deviation for 5×10^{-6} mol/L bromide standard was 1.23% and for 0.25×10^{-3} mol/L it was 0.11% ($n = 6$). In this optimized system, the limit of detection was 5×10^{-8} mol/L bromide, determined as the signal-to-noise ratio (3:1) [27]. The limit of quantification was 1.65×10^{-7} mol/L of bromide, determined as the signal-to-noise ratio (10:1) [27].

After optimization the method was applied to bromide determination in pharmaceutically active substances, water samples and organic substances.

Sample Preparation

Water samples were collected according to the standard procedure (JUS ISO 5667-2:1997) from the following locations: Well K6 (sample 1), raw water (sample 2), water after sand filter (sample 3), water after active coal (sample 4), technical water before active coal (sample 5) and technical water after active coal (sample 6). Samples (37.50 ml volumes) were diluted with 9 mol/L sulphuric acid so that the total concentration of the acid was 2 mol/L in a 50.0 ml normal flask and were well stirred to expell CO_2 that could interfere with determination. Results are shown in Table 1.

Samples of organic substances (TMB-4 (1,1'-(propane-1,3-diyl) bis(4-hydroxyimino methyl) pyridinium dibromide) (synthesized in "Laboratory for organic chemistry and biochemistry," Zagreb, Croatia) and tet-

Table 1. Results of bromide determination in various water samples.

Water samples	FIA [mgBr/L \pm SD]
Sample 1	1.127 \pm 0.013
Sample 2	1.018 \pm 0.010
Sample 3	0.776 \pm 0.008
Sample 4	1.030 \pm 0.010
Sample 5	0.473 \pm 0.004
Sample 6	0.473 \pm 0.004

Table 2. Results of bromide determination in organic substance samples.

Organic substance	Weighed substance	Bromide	FIA method Found		Spectrophotometry Found	
	[mg]		[mg]	[mg]	[%]	[mg]
TMB 4	10.000	3.577	3.626 \pm 0.019	101.37	3.571 \pm 0.031	99.84
(Et) ₄ NBr	10.000	3.807	3.799 \pm 0.019	99.80	3.768 \pm 0.032	98.97

Table 3. Results of bromide determination in pharmacologically active substances and preparations.

Analyzed substances	Weighed [mg]	Br ⁻ [mg]	FIA method		Spectrophotometry		Pharmacopoeia [%]
			Found [mg ± SD]	Recovery [%]	Found [mg ± SD]	Recovery [%]	
FHBr1	10.000	2.081	2.086 ± 0.011	100.26	2.068 ± 0.018	99.37	99.0 – 101.0
FHBr2	10.000	2.081	2.086 ± 0.011	100.26	2.068 ± 0.018	99.37	99.0 – 101.0
IPBr	10.000	1.858	1.850 ± 0.009	99.57	1.792 ± 0.015	96.44	99.0 – 100.5
PANBr	10.000	2.184	2.185 ± 0.011	100.05	2.101 ± 0.018	96.20	98.0 – 102.0
VBr	15.000	1.883	1.868 ± 0.009	99.21	1.838 ± 0.016	97.63	98.0 – 102.0
Atrovent		0.929	0.897 ± 0.005	96.55	0.896 ± 0.008	96.50	100 ± 10
Pavulon		1.001	0.915 ± 0.005	91.43	0.911 ± 0.008	91.04	100 ± 10
Norkuron		0.874	0.846 ± 0.004	96.77	0.839 ± 0.007	96.00	100 ± 10
Partusisten		1.041	1.036 ± 0.005	99.50	0.954 ± 0.008	91.71	100 ± 10

raethyl ammonium bromide (Aldrich, Milwaukee, SAD) were dried at 105°C and 10 mg of each, after weighing on analytical microbalance (accuracy ± 0.001 mg) were dissolved in 100 mL volumetric flask so that bromide concentration corresponded with calibration curve. Results were presented in Table 2.

Active substances (fenoterol hydrobromide, ipratropium bromide and pancuronium bromide) were also dried at 105°C and 10 mg of each, after weighing on analytical microbalance (accuracy ± 0.001 mg) were dissolved in 100 mL volumetric flask so that bromide concentration corresponded with calibration curve. For vecuronium bromide analysis 15 mg of substance was weighed. Results were presented in Table 3.

Pharmaceutical preparation samples were prepared in the following manner: ten Partusisten tablets (same lot) were randomly chosen, crushed and powdered, dried, dissolved in water and quantitatively transferred into 100 mL volumetric flask. One of each ampoule (Norkuron and Pavulon) was randomly chosen from the same lot and quantitatively transferred into 50 mL volumetric flask. Two ampoules of Atrovent were randomly chosen, quantitatively transferred into 10 mL volumetric flask. All solutions were made in 2 mol/L sulphuric acid.

Determination of Bromide Content in Pharmaceutical Preparations

Bromide content was determined in pharmaceutical active substances: fenoterol hydrobromide (FHBr) (manufacturer "Zdravlje", Leskovac, Serbia, signed as FHBr1 and reference material FHBr2, "European Pharmacopoeia", Strassbourg, France), Ipratropium bromide (IPr) ("Zdravlje", Leskovac, Serbia), pancuronium bromide (PANBr) ("European Pharmacopoeia", Strassbourg, France), vecuronium bromide (VBr) ("Zdravlje",

Leskovac, Serbia); and in pharmaceutical preparations: Partusisten (5 mg tablets, "Boehringer Ingelheim", active substance was fenoterol hydrobromide), Atrovent (2 mL ampoule, "Boehringer Ingelheim", active substance was ipratropium bromide), Pavulon (4 mg ampoule, "Organon Tehnika", active substance was pancuronium bromide) and Norkuron (4 mg ampoule, "Organon Tehnika", active substance was vecuronium bromide).

Results were presented in Table 3. Accuracy of evaluated FIA method was checked with reference spectrophotometric method [1] and the methods from European Pharmacopoeia [23, 24].

Conclusions

A fast, simple and sensitive FIA method was optimized for bromide determination in samples: water, pharmaceutical preparations and organic substances. By detailed experiments and the use of cyclic voltammetry as additional method it was concluded that use of potassium bromate as oxidation reagent enabled better sensitivity and lower detection limit. Low detection limits for bromide determination (5×10^{-8} mol/L) allowed their determination in samples with low content of those analytes. The method enabled determination of 60 samples per hour. Preparation of the sample was fast and simple, without complicated operations. Great advantages of this method were saving of reagents and samples, as well as minimal waste. This method could be used as routine analyses in the pharmaceutical industry.

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