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Determination of iodide by detection of iodine using gas-diffusion flow injection and chemiluminescence

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Abstract

This work describes development of a flow injection (FI) system for determination of iodide, based on the chemiluminescence (CL) reaction between iodine and luminol. Iodide in the sample zone is oxidized to iodine. Employment of a gas-diffusion (GD) unit allows for selective detection of the generated CL (425 nm). Preliminary results showed for concentrations of less than 2 mg L^{-1}, that signals were irreproducible and that the calibration was not linear.

In order to solve these problems, a method of 'membrane conditioning' was investigated, in which iodide stream was continuously merged with oxidant to generate I_2 that conditioned the GD membrane and tubing. This minimized surface interaction between the active surface and the I_2 generated from the samples, thus improving both precision and sensitivity. By employing membrane conditioning, it has been possible to reliably detect concentrations down to 0.1 mg L^{-1}.

At the optimized condition, an excellent linear calibration (r^2 = 0.999) was obtained from 0.1 to 1.0 mg L^{-1}. The method was successfully applied to determine iodide in some pharmaceutical products such as potassium iodide tablets and a liquid patent medicine. However, for vitamin tablets, ascorbic acid was found to interfere seriously by causing a negative signal.

Keywords: Chemiluminescence; Gas-diffusion; Iodide; Flow injection; Pharmaceutical products

1. Introduction

Iodine is an essential nutrient in the human diet. Iodine compounds are found in many foods, both naturally and added as supplements. Iodine compounds are also used in preparations of some pharmaceutical products. For example, iodine in the form of tri-iodide is used as antiseptic and disinfectant, while potassium iodide is thought to act as an expectorant. Iodine, mostly in the form of potassium iodide, is also used as an ingredient in multi-vitamin supplements. In the United States, potassium iodide is available in tablet form and sold in drug store for thyroid protection, in the event of nuclear emergency.

However, the level of iodine should be used with extreme caution in cases where patients are markedly sensitive to iodide [1]. In patients with hyperthyroidism, iodide rapidly inhibits the synthesis of thyroid hormones. Therefore, it is essential to have accurate and precise methods available to determine the iodine content of these pharmaceutical products.

Flow injection (FI) analysis [2] is a technique that provides the means of achieving reproducible automated analyses, and there have been several reports in the literature of the use of FI methods for the determination of iodide based on spectrophotometric [3], potentiometric [4], catalytic spectrophotometric [5–10] and flame atomic absorption spectrophotometric [11] detection methods. Determinations based on chemiluminescence (CL) emission from the iodine–luminol reaction have also been reported [12–15]. CL detection is attractive

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in terms of the relatively low cost of the equipment involved and the simplicity of the detection system. Moreover, the CL method permits very low detection limit for iodine down to 1×10^{-7} M [12]. Iodide does not react with luminol, and it is therefore necessary to first oxidize iodide to elementary iodine, in order to initiate chemiluminescence. According to previous reports, this CL detection may be susceptible to a number of interferences including metal ions, and for this reason, a separation technique is usually carried out before the analysis of real samples [13,14].

Burguera and others have reported use of a headspace device coupled to a FI system to separate iodine from the matrix before CL detection [13]. Fujiwara et al. proposed the use of on-line oxidation and solvent extraction coupled with reversed micellar mediated CL detection for determination of iodine and iodide in commercial gargle products [15]. In their work, oxidation of iodide to iodine and solvent extraction of iodine were performed simultaneously before CL detection using the reaction of iodine with luminol in a reversed micellar solution of hexadecyltrimethylammonium chloride.

Normally, by incorporating gas-diffusion (GD) into a FI system, volatile analytes can be separated from interferents in the sample matrix via diffusion across the hydrophobic membrane. This process is fairly selective because fewer species are converted to the gaseous form at room temperature [16]. Motomitzu and Yoden, for example, have reported the use of a tubular GD unit for determination of iodide and other halides [17], and Hakedal and Egeberg [18] used a GD–FI system for determination of iodide in brine. In this latter system, the absorbance of tri-iodide in the UV-region was measured for calibration.

We recently reported work based on the use of GD with a flow injection system for quantitative analysis of iodide [19]. However, the sensitivity of this system was limited by the photometric detection of the I_3^-–starch complex, and therefore in this present work, we have utilized the CL reaction between iodine and luminol as the means of detection. Some problems, which are caused by the chemical properties of iodine and the membrane, are described along with appropriate solutions. The potential of the CL–FI system for quantitative analysis of iodide in pharmaceutical samples is presented.

2. Experimental

2.1. The FI manifold

Fig. 1 depicts two FI systems, which were used in the method development. An AS-90 series autosampler (Perkin-Elmer, USA) was used for automatically loading standard or sample solutions into a 300 μl PTFE loop (1.0 mm i.d.). A FIAS-300 module (Perkin-Elmer, USA) was employed for pumping the reagents. A Metrohm gas-diffusion unit (model 754, Switzerland), fitted inside with a circular PTFE membrane (47 mm i.d., 0.8 mm thickness with pore size 0.45 μm; Sartorius, Germany), was employed. The unit consisted of

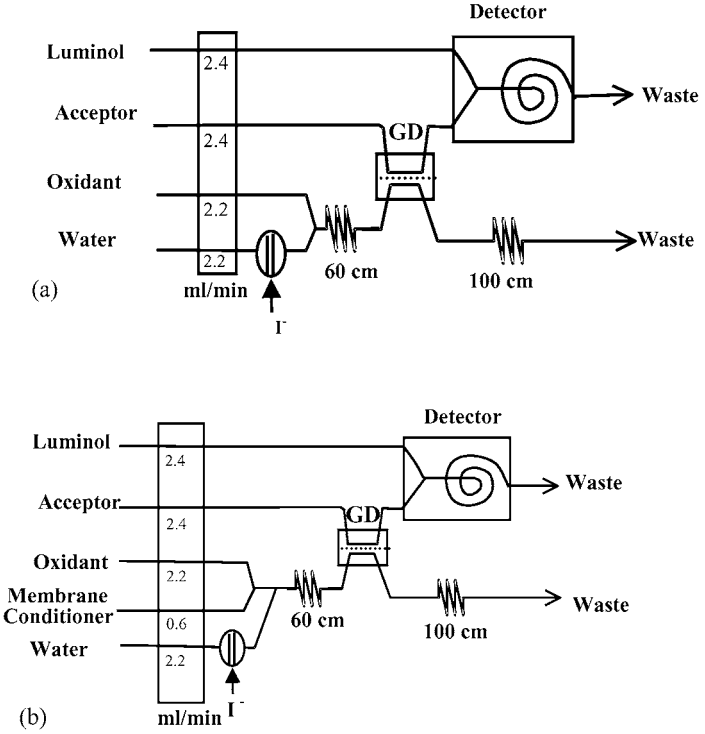

Fig. 1. Flow injection manifold used (a) in the preliminary method for determination of iodide and (b) applied to real sample analysis. Luminol: 7.5×10^{-4} M luminol in 0.1 M NaOH, Acceptor: 2% (w/v) KI solution, Oxidant: 0.01 M $K_2Cr_2O_7$ in 15% (v/v) H_2SO_4, Membrane conditioner: KI solution at 2 mg L^{-1}, GD: gas-diffusion unit, Detector: photomultiplier tube with a home-made flow cell.

two perspex blocks, each has a concentric spiral groove (2 mm × 300 mm × 0.2 mm: width × length × depth). The system shown in Fig. 1a was used in preliminary studies, and this was later modified (Fig. 1b) by adding a line that permitted a continuous flow of an iodide solution through the system for an on-line membrane conditioning. By using this system, the life of the membrane is about 1 week.

A home-made CL detector, used for monitoring the CL light from iodine–luminol reaction, consisted of a concentric spiral PFA (0.75 mm i.d., 100 cm length) flow cell fitted in front of the PMT (Oriel 7020 Photomultiplier, USA). PTFE tubing with i.d. 0.75 mm was used for construction of the two FI manifolds.

2.2. Reagents

2.2.1. Flow injection

All chemicals were of analytical reagent grade. Deionized-distilled water was used for chemical preparation. A stock solution of iodide (1000 mg L^{-1}) was prepared by dissolving 1.307 g (accurate weight) of potassium iodide crystal (Merck, Germany) in 1 L of water. Working standards of iodide were obtained by appropriate dilution with water.

Luminol solution (7.5×10^{-4} M) was prepared in 0.1 M NaOH solution from 3-amino-2,3-dihydro-1,4-phathalazinedione (Sigma, USA) without further purification.

The oxidant was prepared by dissolving 3 g of potassium dichromate (Univar, Australia) in 1 L of 15% (v/v) sulfuric acid (Lab-scan, Ireland).

2.2.2. Potentiometric analysis

Potassium iodide standards for the calibration were prepared from the same stock of iodide solution that was prepared for the FI analysis (1000 mg L^{-1}). Sodium nitrate (5 M), the ionic strength adjuster, was prepared by dissolving 42.5 g of crystal sodium nitrate (Fluka, Switzerland) in 100 mL of water.

2.2.3. Samples

Potassium iodide tablets, for nuclear emergency, were used in the method validation. NO-RAD™ (distributed by Body Gold, USA) and RAD BLOCK KI™ (USDPI, USA) are the samples, which contain 65 mg KI per tablet. IOSAT™ (ANBEX, USA) and Thyro-Block™ (Wallace Pharmaceuticals, USA), both contain 130 mg KI per tablet. Tablets were dissolved in deionized-distilled water, and particulate removed by filtration through Whatman filter paper No. 1 before analysis.

The medicinal sample, Mixt. Stramonium Co., is produced by the Government Pharmaceutical Organization, Bangkok, Thailand. The sample was diluted (16,000 times) before analysis.

2.2.4. Potentiometric method

Accurate 30.0 mL of a sample solution was transferred into a 50 mL beaker. To this sample, 0.6 mL aliquot of sodium nitrate solution (5 M) was added for controlling the ionic strength. The solution was measured for the potential developed across the Orion iodide-ISE (model 9453, USA) and an Orion saturated calomel electrode. A digital Ionanalyzer of Orion (model 601A, USA) was used for this measurement. The operation of this technique was carried accordingly to the instruction manual [20]. Calibration was carried out with standard solutions (1–1000 mg L^{-1}), made from the potassium iodide stock solution (1000 mg L^{-1}).

3. Results and discussion

3.1. Manifold design

A gas-diffusion flow injection (GD–FI) system, shown in Fig. 1a, was investigated for determination of iodide. By means of this system, iodide (I^-) in a sample is oxidized to iodine (I_2) in a donor stream (oxidant + water). Iodine thus formed diffuses through the PTFE membrane into an acceptor stream of iodide solution, and then reacts with a stream of luminol to produce chemiluminescence. While this chemiluminescence reaction is not selective for iodine, the use of membrane diffusion should eliminate interferences in the luminol step.

3.1.1. Problems of non-linearity and irreproducibility

The system in Fig. 1a gave a linear calibration only for the relatively high concentration range (from 2 to 8 mg L^{-1}), whereas at lower concentrations, this was not the case (Fig. 2). The upward curving calibration plot suggested that some kind of adsorption process was occurring. Furthermore, for low

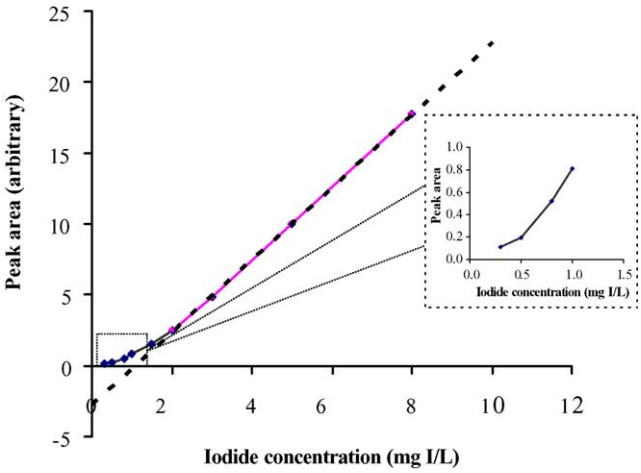

Fig. 2. Illustration of the problem of the first FI manifold (Fig. 1a) which gave non-linear calibration in the low concentration of iodide standards (see enlargement in the inset figure). The dashed line is the best fit with the linear function: $y = 2.55X - 2.70$ ($r^2 = 0.999$), obtained from the data points between 2 and 8 mg I L^{-1}.

concentrations of iodide (<1 mg L^{-1}), the signal was always low for the first injection, and increased gradually with subsequent injections reaching a constant value after the third injection. This behavior was less pronounced at concentrations greater than 6 mg L^{-1}.

We propose the following explanation for the observed non-linearity and poor precision. Iodine (I_2) which is a non-polar compound (compared to water) tends to adsorb to the surface or inside the pores of membrane, which is hydrophobic. Adsorption of elementary iodine may also occur on the surface of the hydrophobic PTFE tubing, basically on the donor side starting from the first merging point in Fig. 1a (oxidant + iodide zone) all the way to waste. Adsorption on the tube walls would also occur on the acceptor side starting from the membrane downstream to waste even that KI is present in the acceptor stream.

Sorption of iodine on tube wall and membrane is expected to be irregular at the start of operation, but once the available hydrophobic surfaces are fully covered with molecular iodine, then the results become reproducible.

In order to take this surface interaction into consideration, we added an extra stream of iodide solution (1 mg L^{-1}) to the FI system. This iodide stream is denoted as "membrane conditioner" in the modified system as shown in Fig. 1b. The purpose of placing a stream of potassium iodide (Fig. 1b) was to continuously produce iodine molecules from the dichromate oxidation. The generated iodine is adsorbed or covers the entire active surface of membrane and plastic tube walls. In this way, iodine that comes from the sample can freely pass through the membrane with negligible loss from adsorption. This modified system gave a better performance producing a linear calibration (r^2 = 0.998) over the entire concentration range (0.1–8 mg L^{-1}).

Preliminary results obtained from employment of the modified system (Fig. 1b) clearly demonstrate that use of membrane conditioning was necessary if measurements were to be made at lower concentrations (≤1 mg L^{-1}). With the membrane conditioner, linear calibration can be achieved and the precision can be improved. However, optimization of concentration of potassium iodide in the conditioning solution should be carried out.

3.2. System optimization

3.2.1. Membrane conditioning

We tested four concentrations of potassium iodide stream as the conditioning reagent (0.5, 1, 2 and 3 mg L^{-1}). Iodide concentrations ≥1 mg L^{-1} gave satisfactorily linear regressions ($0.998 \leq r^2 \leq 0.999$), whereas the lowest concentration of the conditioner did not give linear calibration responses, presumably because membrane conditioning was incomplete.

Fig. 3a clearly illustrates that the sensitivity (slope) increased with increasing iodide concentration in the conditioning reagent. As expected, the level of baseline was elevated with increasing concentration of the iodide conditioner (Fig. 3b). We have observed that the baseline was sometimes quite noisy at the highest concentration (3 mg L^{-1}). This noisy baseline was probably a result of over conditioning, caused by non-uniform adsorption of iodine onto the membrane, which occurs when an excess quantity of iodine is generated for an extended period. Therefore, we chose 2 mg L^{-1} as the optimum concentration for preparing the membrane conditioner.

3.2.2. Acceptor stream conditions

Potassium iodide solution was also used as the acceptor stream (Fig. 1) to promote solubility of iodine, after its diffusion through the membrane. Peak area increased with increasing concentration of potassium iodide up to 2% (w/v). Under conditions of excess of iodide, tri-iodide (I_3^-) rather than I_2 is predominant. However, tri-iodide does not react with luminol to produce the CL. Our results agree with this prediction. We observed that there was less CL intensity when increase in the iodide concentration was greater than 2% (w/v). Hence,

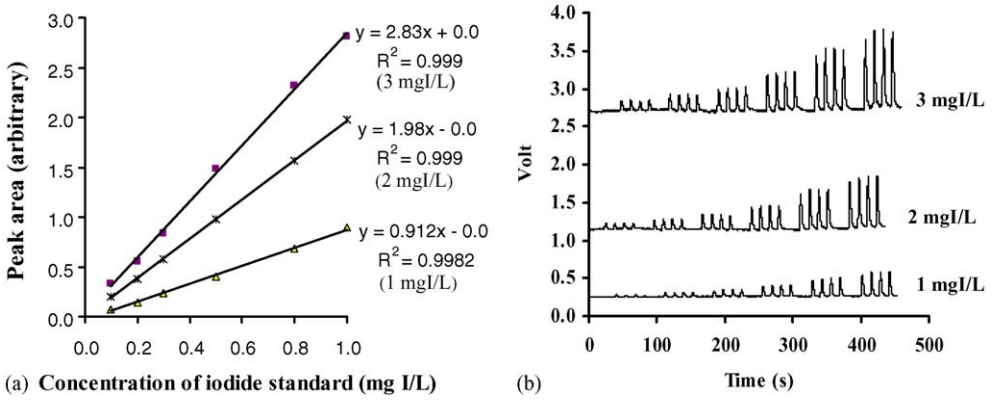

Fig. 3. (a) Examples of the calibration curves obtained at three concentrations of the iodide-conditioning stream (1, 2 and 3 mg I L^{-1}). (b) The FI profiles obtained from replicate injections of six standard solutions of iodide (0.1, 0.2, 0.3, 0.5, 0.8 and 1.0 mg L^{-1}), when performed using the three concentrations of iodide conditioners.

Table 1
Summary of the characteristic of the gas-diffusion FI systems: (a) Chemiluminescence detection (present) and (b) visible detection of I_3^-–starch (former, [19])

Feature	Gas-diffusion FI method with detection of	
	Chemiluminescence (this work)	Visible absorption
1. Working range (mg L^{-1})	0.1–1.0	50–300
2. Sample throughput	high (60 injections h^-)	Relatively low (30 injections h^-)
3. Does the method require a step of 'system cleaning'?	No	Yes
4. Precision (RSD), n = 10	4.8% (For 0.5 mg L^{-1})	1.27% (For 100 mg L^{-1})
5. Availability of detector	Rather limited	Widely available
6. Chemical expense	Expensive (luminol only)	Relatively low cost (all chemicals)
7. Does the system require 'membrane conditioning'?	Yes	No

2% (w/v) potassium iodide was chosen as the appropriate condition for the acceptor solution.

The luminol concentration was also optimized for the most intense signal using a concentration range of 5×10^{-4} to 4×10^{-3} M luminol, and the concentration of 7.5×10^{-4} M was chosen.

The effect of pH on the CL reaction is critical. pH of the luminol stream was varied from 11 to 13 in increments of 0.5 pH unit. The stream's pH was adjusted using a sodium hydroxide solution. The optimal pH for the reaction under our experimental condition was 12.

Since a potassium dichromate solution is stable and has an appropriate standard oxidation–reduction potential for the oxidation of iodide to iodine, it was selected as the oxidizing agent in this work. The concentration of potassium dichromate, within the studied range (0.005–0.05 M $K_2Cr_2O_7$), had very little effect on the CL signal, and 0.01 M $K_2Cr_2O_7$ in 15% (v/v) sulfuric acid was used in all subsequent experiments

3.3. Analytical performance and comparison with the previous system

Under optimized conditions, the calibration is always linear within the concentration range 0.1–1.0 mg L^{-1}.

While the manifold used in this system is similar to a previous one that utilized visible absorption of the I_3^-–starch complex for detection [19], this new manifold offers some definite improvements in analytical performance, as summarized in Table 1. The CL detection method provides much improved sensitivity compared with the previous system. It also avoids the need for a "cleaning" step that was necessary to prevent the deposition of the I_3^-–starch complex on tube wall and the flow cell, which cause irreproducible signals. And as a result, the sample throughput is twice that of the I_3^-–starch system.

The precision of the system described was 4.8% for 0.5 mg L^{-1}, whereas the precision of the previous system was 1.27% for 100 mg L^{-1}. Note that the iodide concentration used in these two systems was quite different because of the differing sensitivities of the two systems.

3.4. Application to pharmaceutical products

Four samples of potassium iodide tablets (for protection against thyroid absorption of radioactive iodine) were analyzed for iodide contents. There was also a product of the Thai Government Pharmaceutical (Mixt. Stramonium Co.) for bronchial asthma. The analyzed iodine contents were compared with the values measured by the ISE method (Table 2), using paired t-test. The results indicated that the contents of iodide as determined from the two methods agree significantly well with each other ($t_{observed}$ = 0.36, $t_{critical}$ = 2.77 at P = 0.05). The experimental results (FI and ISE) also agree with the nominal values.

3.5. Interference studies

The GD–FI system was also used to determine iodide in more complicated matrices, such as multi-vitamin tablets.

Table 2
Determination of iodide contents in pharmaceutical products by using the present FI method and the ISE method

Trade name	Sample type	Concentration unit	Iodide content		
			Nominal	Our FI method (Fig. 1b)	ISE
1. NO-RAD[a]	KI tablet	mg I per tablet	49.7	53.2 ± 7.6	57.9 ± 7.3
2. RAD BLOCK KI[b]	KI tablet	mg I per tablet	49.7	50.0 ± 0.3	51.3 ± 0.5
3. IOSAT[c]	KI tablet	mg I per tablet	99.5	97.6 ± 1.4	101.1 ± 5.5
4.Thyro-Block[c]	KI tablet	mg I per tablet	99.5	99.8 ± 0.7	99.8 ± 2.7
5. Mixt. Stramonium Co.	Liquid patent medicine	mg I L^{-1}	183	192.3 ± 8.2	186.2 ± 6.7

The means and standard errors were from a set of three samples of the same product.
[a] 0.25 g (Weight of the tablet).
[b] 0.30 g (Weight of the tablet).
[c] 0.17 g (Weight of the tablet).

The results indicated that three out of four multi-vitamin samples gave negative signals when using the FI method. We surmise that the origin of the negative peaks is due to the presence of ascorbic acid, or some other reductants in the sample matrix, that inhibits the formation of iodine in the conditioning reagent, or even actively removes iodine from the conditioned tubing and membrane surfaces.

To determine the origins of this interference, we investigated the effects of metal ions and vitamins that are present in vitamin extracts (i.e., vitamin B complex, vitamin C and some cations such as Mn^{2+}, Zn^{2+} and K^{+}). These substances were added into a standard iodide solution (0.5 mg L^{-1}) at the levels which are twice than the normal concentrations in the sample extracts (40, 4, 2 and 0.02 mg L^{-1} of vitamin B1, B2, B6 and B12, respectively, and 15, 50 and 15 mg L^{-1} of Mn^{2+}, Zn^{2+} and K^{+}, respectively). The results of these tests explicitly show that the presence of vitamin C (added as ascorbic acid) resulted in negative signal profiles (for example, −68% signal alteration, at 0.5 mg L^{-1}). Other tested substances did not exhibit such a marked effect.

The evidence has shown that vitamin C, which is easily extracted by water, interferes seriously in our method. Increasing in concentration of the dichromate oxidant or even with off-line premixing with oxidant did not show any improvement in eliminating the interfering effect of ascorbic acid. Other means of pretreatment, perhaps by separation, is necessary for sample extracts that contain vitamin C.

4. Conclusions

In this work, a flow injection system, which employs gas-diffusion unit for selective detection of iodide, was developed. Dynamic conditioning of the system by continuous oxidation of iodide to provide a constant background of iodine was found necessary to achieve a linear calibration. This type of system conditioning can be optimized to obtain the desired sensitivity. Generally, this method is sensitive and simple. The present method was successfully applied to determine iodide in KI tablets and in a liquid medicine, but significant signal suppression was observed in multi-vitamin samples containing high concentrations of ascorbic acid. Studies of suitable pretreatment options for samples containing ascorbic acid are in progress.

Acknowledgements

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