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Sensitive determination of epinephrine in pharmaceutical preparation by flow injection coupled with chemiluminescence detection and mechanism study

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ABSTRACT: A novel, rapid and sensitive method was described for the determination of epinephrine (EP) using flow injection analysis coupled with chemiluminescence (CL) detection, which based on EP enhanced the weak CL emission of luminol–KIO_4 system in NaOH solution. Parameters affecting the CL intensity and reproducibility were optimized systematically. Under the optimized experiment conditions, the net CL intensity was proportional to the concentration of EP in the range of 5.0×10^{-8} to 1.5×10^{-6} mol/L with a detection limit of 1.9×10^{-9} mol/L. The relative standard deviation (RSD) was found to be 0.7% for 13 replicate determinations of 3.0×10^{-7} mol/L EP. The applicability of the proposed method was illustrated in the determination of EP in pharmaceutical preparation. The recoveries of EP at different levels in EP hydrochloride injection were between 95.4 and 104.7%. One assay procedure takes only 27 s, and the sampling rate was calculated about to be 130 samples/h. The possible mechanism of the enhanced CL intensity was studied by examining CL spectra and UV–vis spectra. Copyright ©2009 John Wiley & Sons, Ltd.

Keywords: chemiluminescence; flow-injection; epinephrine; mechanism study

Introduction

Epinephrine (EP) or adrenaline, 1-(3, 4-dihydroxyphenyl)-2-methyloamino-ethanol, belongs to the catecholamine family and plays an important role as neurotransmitters and hormones (1). It is biosynthesized in the adrenal medulla and sympathetic nerve terminals, as well as beings secreted by the suprarenal gland along with norepinephrine. It was first isolated in 1901 by Takamine and Aldrich, and was synthesized in 1904 by Stolz and Dalkin (2). Medically, it is used in the treatment of heart attack, bronchial asthma and cardiac surgery (3). Therefore, the determination of EP in biological fluids or pharmaceutical preparation is very important. Different methods have been reported to determine EP, such as ultraviolet and visible spectrophotometry (UV–vis) (4,5), fluorimetry (6), liquid chromatographic liquid (7), capillary electrophoresis (8,9), amperometric (10), biamperometry (11), piezoelectric detection (12) and various sensors (1,13).

Flow injection analysis (FIA) is a high-efficiency analytical technique and offers advantages in terms of simplicity, high efficiency, good reproducibility, low cost and short analysis time (14,15). The commonly used detection modes for FIA are UV–vis (16), laser-induced fluorescence (LIF) (17) and fluorescence (18). Although LIF detection has the advantage of high sensitivity, the disadvantages are expensive instrumentation and complicated approach. UV detection is most commonly used in FIA, but the concentration limit of detection (LOD) is relatively high. In comparison with these detection modes, chemiluminescence (CL) detection has been proven to be one of the most powerful techniques for the analysis of various analytes including metal ions (19,20), biological matrices (21–25), and pharmaceutical preparations (26,27) owing to its high sensitivity and simplicity, and has been used in the determination of EP (28–30). Analytical procedures applying CL detection in FIA setups integrated the advantages of simplicity, rapidity and reproducibility, and were appropriate for on-line analysis (31,32). However, most of the FIA-CL methods for the determination of EP employ indirect CL detection. Sun *et al*. (33) reported an FIA-CL procedure for the analysis of catecholamines including EP, based on its restraining effect on CL intensity of luminol–potassium chlorate system.

In this work, we found that the CL emission of luminol–KIO_4 system can be greatly enhanced by EP in NaOH solution. Based on this phenomenon, a new, rapid and sensitive FIA-CL method for the analysis of EP was proposed. The conditions for the CL emission and reproducibility were investigated systematically. The proposed method was applied successfully to the determination of EP in pharmaceutical preparations. The possible mechanism of EP-enhanced luminol–KIO_4 CL reaction was discussed.

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Experimental

Chemicals and reagents

The 10 mmol/L stock solution of luminol (3-aminophthalhydrazide, Suzhou Yacoo Chemical Factory, China) was prepared by dissolving luminol in 0.1 mol/L NaOH solution. The 10 mmol/L stock solution of EP was prepared by dissolving of 22 mg EP (Sigma, USA) in 10 mL pure water. Both the stock solutions of EP and luminol were stored in the refrigerator at 4°C. Working solutions of luminol were prepared daily from the stock solution of luminol by appropriate dilution with NaOH solution. KIO_4 and NaOH were purchased from Beijing Xihui Chemical Factory (Beijing, China) and Tianjin Kaitong Chemical Reagent Co. Ltd, respectively. All the chemicals and reagents were of analytical-reagent grade and used without further purification unless specified otherwise. The water used was pure water (18.2 MΩ.cm) processed with an Ultrapure Water System (Kangning Water Treatment Solution Provider, China). The EP hydrochloride injection (H12020526) was produced at Tianjin Golden Amino acid Co. Ltd (Tianjin, China).

Apparatus and instrumentation

The FIA-CL cell was constructed in combination with a model IFFM-E FIA system (Xi'an Remax Analytical Instrument Co. Ltd, China) for this work, as shown in Fig. 1. It consisted of two peristaltic pumps (P_1, P_2), a switching valve (S), two Y-shaped mixture valves (Y_1, Y_2), a flow cell (F) and a CL detector (photomultiplier tube, PMT). All components in the flow system were connected with polytetrafluoroethylene (PTFE) tubes (0.8 mm i.d.). A flat spiral-coiled colorless silicon rubber tube (i.d. 0.8 mm; total length of the flow cell, 6 cm, without gaps between tubes) was used as flow cell and was placed in front of the PMT, which was biased at −600 V for measurement. Both the flow cell and the PMT were mounted within a light-tight steel box. The CL signal was transferred into a computer automatically, which employed FIA-CL system software. CL spectra were measured with a Cary Eclipse fluorescence spectrophotometer (Varian, USA). UV–vis spectra were taken by the Uvmini-1240 UV-vis spectrophotometer (Shimadzu, Japan).

Procedure

One assay procedure included two steps in this FIA-CL mode. In the first step of 2 s, water carrier and blank (or sample) solution were introduced into the flow line by pump P_1 at a constant speed of 0.68 mL/min when the direction of the switching valve was in the load position. At the same time, the solutions of luminol and KIO_4 were pumped by P_2 at the 1.14 mL/min. During the second step of 25 s, switching valve, P_1 and P_2 worked simultaneously. The direction of the switching valve was changed to the detection position. Water carrier and blank (or sample) were pumped by P_1 at 1.14 mL/min. Luminol and KIO_4 were pumped by P_2 at the 0.40 mL/min. During the last few seconds of the second step, the direction of the switching valve was changed to the load position, and the sample reacted with the mixture of luminol and KIO_4 in the flow cell to produce CL signal. As mentioned above, EP was found to strongly enhance the weak CL emission of luminol–KIO_4 system. Therefore, the concentration of EP was quantified based upon the net CL intensity changes (ΔI_{CL}), $\Delta I_{CL} = I_S - I_0$, where I_S and I_0 are the CL intensities of the EP and blank solution, respectively.

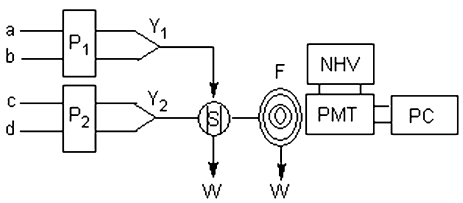

Figure 1. Schematic diagram of the FIA system. (a) Sample or blank solution; (b) H_2O; (c) luminol (in 0.1 mol/L NaOH) solution; (d) KIO_4 solution. P_1 and P_2, peristaltic pumps; S, switching valve; Y_1 and Y_2, confluence points; F, flow cell; W, waste water; PMT, photomultiplier tube; PC, personal computer; NHV, negative high voltage.

Results and discussion

Effect of NaOH concentration

The effect of NaOH concentration on the net CL intensity was investigated in the range of 0–0.3 mol/L and the results are shown in Fig. 2. The experimental results shown that the net CL intensity became stronger with the NaOH concentration increasing in the range 0–0.1 mol/L, and reached the largest ΔI_{CL} when the NaOH concentration was 0.1 mol/L. Further increase of the NaOH concentration decreased net CL intensity. Thus, 0.1 mol/L was chosen as the optimized NaOH concentration.

Effect of luminol concentration

The influence of luminol concentration in 0.1 mol/L NaOH solution on ΔI_{CL} was investigated in the range 1.0×10^{-6} to 2.0×10^{-4} mol/L (shown in Fig. 3). It can be seen (Fig. 3) that the net CL intensity increased as the concentration of luminol increased from 1.0×10^{-6} to 6.0×10^{-5} mol/L; ΔI_{CL} reached the maximum at 6.0×10^{-5} mol/L. However, ΔI_{CL} became stable when the concentration of luminol increased from 6.0×10^{-5} to 2.0×10^{-4} mol/L. Therefore, the concentration of luminol was selected to be 6.0×10^{-5} mol/L.

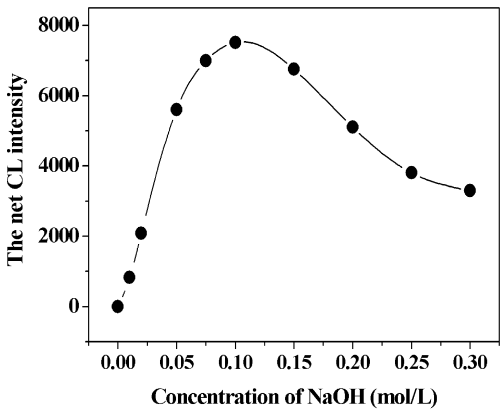

Figure 2. Effect of NaOH concentration. Experimental conditions: luminol, 1.0×10^{-4} mol/L; KIO_4, 1.0×10^{-4} mol/L; EP, 3.0×10^{-7} mol/L.

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Effect of KIO_4 concentration

The dependence of the net CL intensity on the KIO_4 concentration was examined in the range of 2.0×10^{-5} to 3.5×10^{-4} mol/L (as shown in Fig. 4). It was observed that the net CL intensity increased with the KIO_4 concentration up to 1.5×10^{-4} mol/L; further increase of KIO_4 concentration did not cause the net CL intensity increase. Therefore, 1.5×10^{-4} mol/L KIO_4 was used.

Effect of run parameters of FIA system

In order to obtain the higher sensitivity and better reproducibility, the run parameters of FIA-CL system were investigated in detail and the results are listed in Table 1.

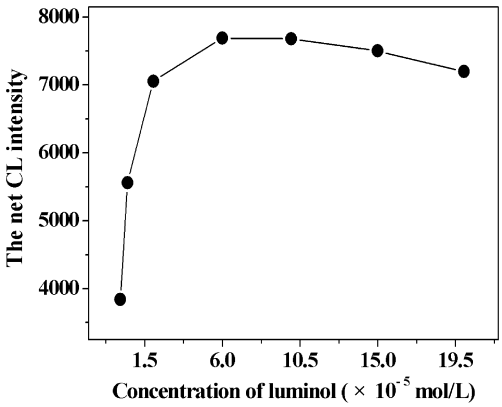

Figure 3. Effect of luminol concentration. Experimental conditions: NaOH, 0.1 mol/L; KIO_4, 1.0×10^{-4} mol/L; EP, 3.0×10^{-7} mol/L.

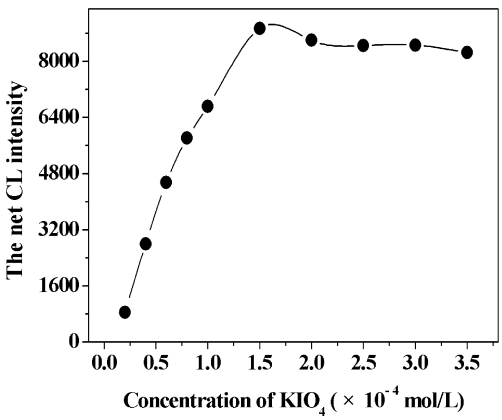

Figure 4. Effect of KIO_4 concentration. Experimental conditions: luminol, 6.0×10^{-5} mol/L; NaOH, 0.1 mol/L; EP, 3.0×10^{-7} mol/L.

Linear response range, RSD and limit of detection

Under the optimum conditions as described above, the calibration graph of ΔI_{CL} vs EP concentrations was linear in the range of 5.0×10^{-8} to 1.5×10^{-6} mol/L. The regression equation was $\Delta I_{CL} = 2.18 \times 10^{10} C - 1519.5$ (where C is the concentration of EP, in mol/L) with a correlation coefficient (r) of 0.9968. According to IUPAC, the LOD was determined from three times the standard deviation of blank signal (3 s) as 1.9×10^{-9} mol/L. The RSD was 0.7% for 13 replicate determinations of 3.0×10^{-7} mol/L EP solution.

In comparison with several reported methods (8–12), the proposed method in this paper offers higher sensitivity and better precision. Moreover, the one assay procedure takes only 27 s. The sampling rate was calculated about to be 130 samples/h.

Interferences study

The effects of possible coexisting compounds in EP hydrochloride injection were evaluated by analyzing standard solutions of EP (3.0×10^{-7} mol/L) to which interference species were added. The tolerance amount and the value (%) of relative error are listed in Table 2. From Table 2, it can be seen that most of substances, such as cations, anions, sodium citrate, citric acid and amino acids, did not affect the determination of EP. The results indicated that the selectivity of the proposed method for determination EP in EP hydrochloride injection is good.

Sample analysis

The proposed method was used in the analysis of EP in epinephrine hydrochloride injection. Table 3 listed the measured results of the content of EP in EP hydrochloride injection, which are very close to the labeled value in EP hydrochloride injection. In addition, the recoveries of EP hydrochloride injection for EP at different spiked concentration levels were found to be in the range of 95.4–104.7%. The RSDs ($n = 11$) for the measurements were in the range 1.0–2.3%. The results indicated that the proposed method is accurate and sensitive enough for the measurement of the EP in pharmaceutical preparation of EP hydrochloride injection.

Mechanism study

As mentioned above, the determination of EP presented in this work was based on EP enhancing the CL emission of the luminol–KIO_4 system in NaOH solution (shown in Fig. 5). The maximum wavelengths of CL emission spectra of luminol–KIO_4 and a analyte-sensitized luminol–KIO_4 maximum at 425 nm have been reported in the literature; 3-aminophthalate ion is thought to be the CL emitter (34,35). In this work, to get an idea about the EP enhancement on luminol–KIO_4 CL reaction, the CL emission

Table 1. Effect of run parameters of FIA-CL system and the optimum values

Step no.	Variable parameters	Range studied	Optimum values
1	Running time (s)	1–5	2
	Flow rate of P_1 (mL/min)	0.23–0.80	0.68
	Flow rate of P_2 (mL/min)	0.28–1.42	1.14
2	Running time (s)	10–35	25
	Flow rate of P_1 (mL/min)	0.57–1.42	1.14
	Flow rate of P_2 (mL/min)	0.06–0.51	0.40

Table 2. Tolerable concentration ratios for interfering species in the analysis of 3.0×10^{-7} mol/L EP

Species added	Mole ratio ($C_{species}/C_{EP}$)	Variation of CL peak height (%)[a]
Na^+	1000	+1.09
K^+	1000	−1.17
Ca^{2+}	100	−5.59
Co^{2+}	50	−4.08
Mg^{2+}	10	+5.47
Fe^{3+}	10	−3.54
Fe^{2+}	10	−3.79
NO^{3-}	1000	+2.56
Cl^-	1000	+1.09
OH^-	500	−0.57
SO_3^{2-}	100	−4.80
Glucose	1000	+0.57
Lactose	1000	+2.29
Sodium citrate	500	+0.99
Ethanoic acid	100	+5.20
Threonine	1000	−0.53
Lysine	1000	−4.23
Cystine	1000	−1.89
Leucine	1000	+1.26
Arginine	1000	+5.06
Alanine	500	−4.76
Valine	500	−0.64
Serine	500	+5.29
Proline	500	+2.50
Isoleucine	100	+3.79

[a]Variation of CL peak height (%): $(I_{species} - I_{EP})/I_{EP}$.

spectra of luminol–KIO_4 CL reaction in the absence and in the presence of EP were examined by a fluorospectrophotometer (turn off the excitation light source) and the results are shown in Fig. 6. The results showed that the maximum emission appeared at 425 nm for the above two CL reactions. This indicated that the luminophor of EP-enhanced luminol–KIO_4 CL reaction is still 3-aminophthalate ions.

Series experiments were performed to determine further details of EP enhancement on the luminol–KIO_4 CL reaction. The UV–vis absorption spectra of EP, KIO_4 and their mixture were studied, respectively. The results (Fig. 7) indicated that the reaction took place according to the fact that the absorption peak of EP at 280 nm disappeared after EP was mixed with KIO_4. When dissolved oxygen was removed by purging pure nitrogen in the reaction of luminol–KIO_4–EP, the CL intensity decreased clearly. The results indicated that the dissolved oxygen plays an important role in the above reaction. It has been shown that epinephrine may react with dissolved oxygen in NaOH solution to produce hydroxyl and/or superoxide radicals. It was also reported that the CL reaction between luminol and KIO_4 could be enhanced greatly in the presence of hydroxyl and/or superoxide radicals (36–38). Based on the above discussion, the possible mechanism of the present CL reaction was suggested to be as follows:

Table 3. Results of the determination of EP in EP hydrochloride injection

EP added (mmol/L)	Labeled (mmol/L)	Found (mmol/L)	Recovery (%)	RSD (%, $n = 11$)
0.00	4.55	4.28	—	1.0
7.50		12.13	104.7	1.7
11.60		15.35	95.4	2.3

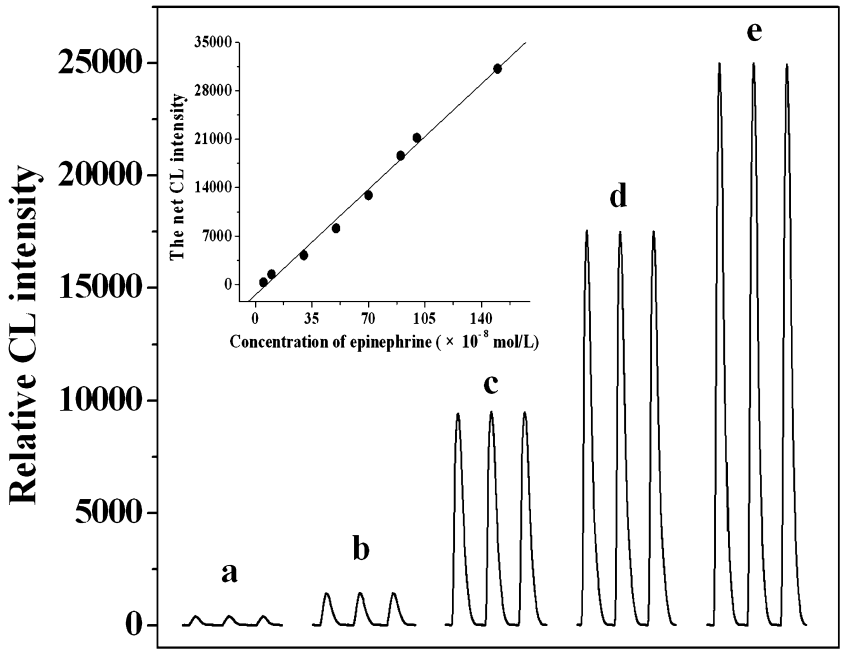

Figure 5. The EP enhancement on luminol–KIO_4 CL reaction: (a) without EP; (b) with 9.0×10^{-8} mol/L EP; (c) with 3.0×10^{-7} mol/L EP; (d) with 5.0×10^{-7} mol/L EP; (e) with 7.0×10^{-7} mol/L EP. Experimental conditions: luminol, 6.0×10^{-5} mol/L; NaOH, 0.1 mol/L; KIO_4, 1.5×10^{-4} mol/L.

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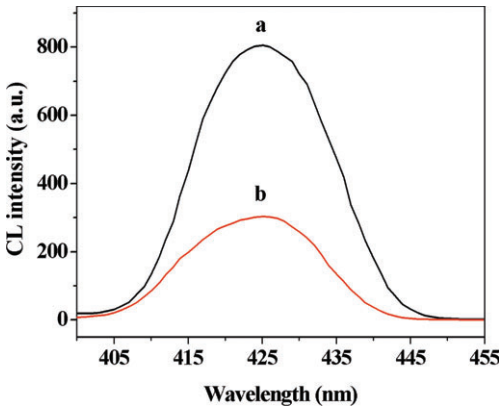

Figure 6. The CL emission spectra of: (a) luminol–KIO_4–NaOH–EP; (b) luminol–KIO_4–NaOH. Experimental conditions: luminol, 6.0×10^{-5} mol/L; NaOH, 0.1 mol/L; KIO_4, 1.5×10^{-4} mol/L; EP, 3.0×10^{-7} mol/L.

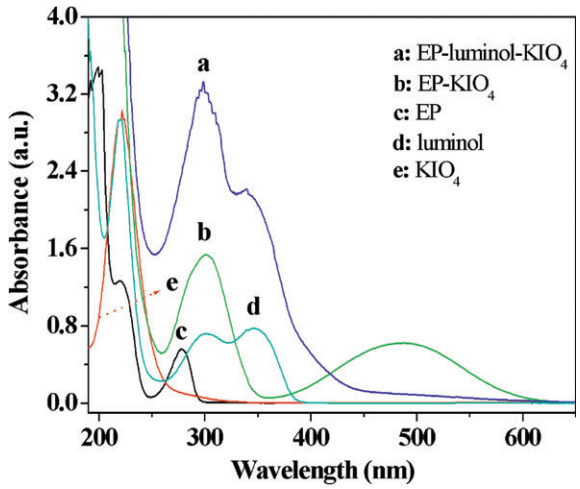

Figure 7. UV–vis spectra of: (a) EP–luminol–KIO_4; (b) EP–KIO_4; (c) EP; (d) luminol; (e) KIO_4. Experimental conditions: luminol, 6.0×10^{-5} mol/L; NaOH, 0.1 mol/L; KIO_4, 1.5×10^{-4} mol/L; EP, 3.0×10^{-7} mol/L.

Epinephrine + dissolved oxygen + NaOH → hydroxyl and/or superoxide radicals + other reaction products

luminol + hydroxyl radicals and/or superoxide radicals + KIO_4 → 3-aminophthalate ion*

3-aminophthalate ion* → 3-aminophthalate ion + $h\nu$ (λ_{max} = 425 nm)

Conclusions

In this work, a new, rapid and sensitive FIA-CL method for the determination of EP was proposed, based on the enhancing effect of EP on the luminol–KIO_4 CL reaction. The results of real sample analysis demonstrate that the proposed FIA-CL method is suitable for the determination of EP in pharmaceutical preparation. The possible mechanism was studied based on the CL spectra and UV–vis spectra, and the emitter of the luminol–KIO_4–EP CL system in NaOH solution is still 3-aminophthalate ions.

Acknowledgments

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