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Determination of L-thyroxine in pharmaceutical preparations by flow injection analysis with chemiluminescence detection based on the enhancement of the luminol–$KMnO_4$ reaction in a micellar medium

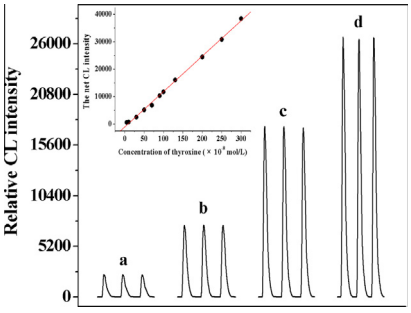
Juntao Cao, Hui Wang, Yanming Liu *

College of Chemistry and Chemical Engineering, Xinyang Normal University, Xinyang 464000, PR China

HIGHLIGHTS

- Flow injection technique coupled with a novel CL system was developed.
- The CL system was luminol–$KMnO_4$ in CTMAB surfactant micelles.
- L-Thyroxine has great signal enhancement on the CL system sensitized by CTMAB.
- The method was applied for the detection of L-thyroxine in commercial tablets.

GRAPHICAL ABSTRACT



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ABSTRACT

A novel flow injection chemiluminescence (CL) method for the determination of L-thyroxine in the presence of cethyltrimethylammonium bromide (CTMAB) surfactant micelles is developed. The method is based on the significant signal enhancement of L-thyroxine on the luminol–$KMnO_4$ system in alkaline solution sensitized by CTMAB. Parameters affecting the reproducibility and CL detection were optimized systematically. Under the optimum conditions, the net CL intensity versus L-thyroxine concentration was linear in the range of 5.0×10^{-8}–3.0×10^{-6} mol/L with the detection limit of 8.9×10^{-9} mol/L. The sample throughput is calculated to be 140 samples/h and the relative standard deviations (RSDs) for 13 replicate determination of 1.0×10^{-6} L-thyroxine is 1.1%. The proposed method was successfully applied for the determination of L-thyroxine in pharmaceutical preparations with satisfactory recoveries in the range of 93.9–105.2%. This rapid, sensitive, and high throughput method would provide a new tool for L-thyroxine analysis.

Introduction

Thyroxine, one tyrosine-based hormone produced by the thyroid gland, which could be secreted directly into the blood stream, plays major biological roles in regulation of metabolism. Deficiency of the hormones leads to goiter, myxoedema and cretinism, while excessive secretion causes Graves's disease (exophthalmic goitre). The important role of thyroxine have led to increasing efforts to establish various methods for the determination of it. Thyroxine has L- and D-forms. L-Form is twice as active physiologically as the racemic product, and L-form has very little activity. The current analytical methods used for thyroxine analysis included mass spectrometry ([1,2], immunoassay including chemiluminescence [3,4], electrochemiluminescence [5], fluorescence [6] and radioimmunoassay [7], and electrochemical techniques [8]. While every

* Corresponding author at: College of Chemistry and Chemical Engineering, Xinyang Normal University, 237 Chang'an Road, Xinyang 464000, PR China. Fax: +86 376 6392889.
E-mail address: liuym9518@sina.com (Y. Liu).

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strategy possesses distinct advantages, each also suffers its own drawbacks such as expensive instrumentation, complicated operation, use of radioactive materials and low sample throughput.

Flow injection with chemiluminescence detection (FI-CL) has received considerable attention with the characteristics of high sensitivity, wide calibration range, satisfactory robustness and rapid analysis [9,10]. Currently, the technique has been successfully applied to the analysis of amino acids [11], protein [12,13], DNA [14], nanoparticles [15] and pharmaceutical preparation [16–18]. Several FI-CL methods have been developed for the thyroxine detection based on $KMnO_4$–Na_2SO_3 [19], luminol–iron(II) [20], luminol–H_2O_2–Co(II) [21], and Ru(bpy)$_3^{3+}$–NADH [22]. However, FI-CL method for the thyroxine detection with a luminol–$KMnO_4$ system has not been reported so far.

Herein, a novel FI-CL method is developed for the thyroxine detection, based on its enhancement effect on the luminol–$KMnO_4$ CL system in presence of cethyltrimethylammonium bromide (CTMAB) surfactant. The conditions for the CL emission and reproducibility were investigated in detail. The proposed method was successfully applied for the determination of L-thyroxine in pharmaceutical thyroxine tablets.

Materials and methods

Chemicals and reagents

Luminol (3-aminophthalhydrazide) was purchased from Suzhou Yacoo Chemical Factory (China). $KMnO_4$ was obtained from Tianjin Chemical Reagent Factory (China). L-Thyroxine was from Sigma (USA). Dodecyl trimethylammonium bromide (DTAB), cethyltrimethylammonium bromide (CTMAB), polyoxyethylene lauryl ether (Brij-35), sodium dodecyl sulfate (SDS), cetyl pyridinium bromide (CPB) and dodecyltrimethylammonium chloride (DTAC) were purchased from Seebio Biothechnology Inc. All the chemicals and reagents were of analytical-reagent grade. Water used was pure water (18.2 MΩ cm) processed with an Ultrapure Water System (Kangning Water Treatment Solution Provider, China). The thyroid tablets (H31022151) was produced at Shanghai Industrial United Group Pharmaceutical Co., Ltd. Great Wall. Levothyroxine Sodium Tablets (H20060090) was purchased from Merck KGaA, Darmstadt.

Apparatus and instrumentation

The FI-CL analysis was performed on a model IFFM-E flow-injection chemiluminescence analyser system (Xi'an Remax Analytical Instrument Co. Ltd., China) .The schematic diagram of the system was shown in Fig. 1. The system consists 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 (PMT). The peristaltic pumps were used to deliver all solutions. The polytetrafluoroethylene (PTFE) tubes (0.8 mm i.d.) was used to connect all the components of the flow system. 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 a photomultiplier (Hamamatsu, Japan) biased for measurement. The CL signal was recorded by using an computer equipped with a FI-CL system software.

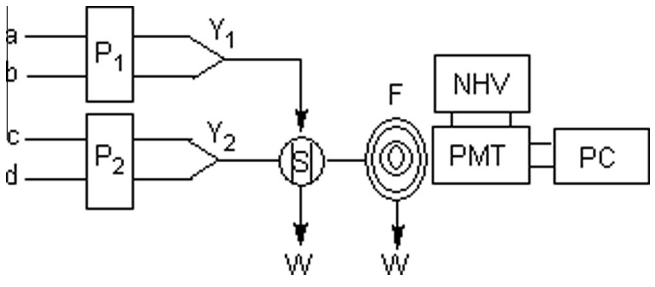

Fig. 1. Scheme of FI-CL system. a, Sample or blank (pure water) solution; b, CTMAB; c, luminol; d, $KMnO_4$; P_1 and P_2, peristaltic pumps; S, switching valve; Y_1 and Y_2, confluence points; F, flow cell; W, waste water; PMT, photomultiplier tube; PC, personal computer; NHV, negative high voltage.

FI-CL procedures

One assay procedure included two steps in this FI-CL mode. In the first step of 5 s, water carrier and blank (or sample) solution were introduced into the flow line by pump P_1 at a constant speed of 1.42 mL/min when the direction of the switching valve was in the load position. At the same time, the solutions of luminol and $KMnO_4$ were pumped by P_2 at the 0.85 mL/min. During the second step of 20 s, switching valve, P_1 and P_2 worked simultaneously. The direction of the switching valve was changed to the sampling position. CTMAB and blank (or sample) were pumped by P_1 at 1.14 mL/min. Luminol and $KMnO_4$ were pumped by P_2 at the 0.85 mL/min. During the last few seconds of the second step, the direction of the switching valve was changed to the load position, sample reacted with the mixture of luminol and $KMnO_4$ in the flow cell to produce CL signal. As mentioned-above, L-thyroxine was found to strongly enhance the weak CL signal of luminol–$KMnO_4$ in NaOH solution. Therefore, the concentration of L-thyroxine 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 peak height of L-thyroxine and blank solution, respectively.

Preparation of drug tablets

Five tablets were weighed and made them powdered and homogenized in a mortar. Based on the labeled amount of the macrolides drugs tablets, an amount of the power was dissolved in 10 mL 0.1 mol/L NaOH solution to obtain a stock solution of 5 mmol/L. Then the stock solutions were centrifuged for 5 min at 2500 rpm to remove deposit.

Results and discussion

Optimization of CL reactions

The type of surfactant used in the experiment was screened and the concentration of surfactant, NaOH, luminol and $KMnO_4$ were optimized for sensitive and precise detection of L-thyroxine in the subsequent experiments. For optimization, the 1.0×10^{-6}-mol/L L-thyroxine was used.

The presence of surfactant in the CL reaction system offered many advantages such as promotion of dissolubility, changing dielectric constant of solution, buildup of stability and further enhanced the CL intensity. The effect of different surfactants including CPB, DTAB, Brij-35, SDS, DTAC and CTMAB on CL intensity were investigated in this work. Experiment results show that only CPB and CTMAB can enhance the CL intensity of this system, and the sensitization of CTMAB is greater than that of CPB. Therefore, CTMAB was selected in the present CL system. And then, the effect of varying CTMAB concentration from 5.0×10^{-5} to 6.0×10^{-4} mol/L was examined (shown in Fig. 2). It was found that the best CL intensity and reproducibility could be obtained in 3.0×10^{-4} mol/L CTMAB. So, 3.0×10^{-4} mol/L CTMAB was used in the subsequent experiments.

The effect of NaOH concentration on the net CL intensity was investigated in the range of 0–0.12 mol/L and the result was depicted in Fig. 3. It can be seen that the net CL intensity increased