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Short communication

Ion-pair complex-based solvent extraction combined with chemiluminescence determination of chlorpromazine hydrochloride with luminol in reverse micelles

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Abstract

A new chemiluminescence (CL) method is proposed for the determination of chlorpromazine hydrochloride, which is based on the dichloromethane solvent extraction of ion-pair complex of tetrachloroaurate(III) with chlorpromazine hydrochloride and luminol chemiluminescence detection in a reversed micellar medium formed by the cation surfactant cetyltrimethylammonium bromide in a dichloromethane–cyclohexane (1:1 V/V)–water (0.3 mol/L Na_2CO_3 buffer solution with the pH of 11.5). The ion-pair complex of tetrachloroaurate(III) with chlorpromazine hydrochloride produced an analytical chemiluminescence signal when it entered the reversed micellar water pool. In the optimum conditions, CL intensities are proportional to concentrations of the studied drug over the range 0.05 ~ 10 μg/mL with a detection limit (DL) of 6 ng/mL. The relative standard deviation (R.S.D.) is 2.6% for 1.25 μg/mL chlorpromazine hydrochloride ($n = 11$). R.S.D. (precision) of inter-day and intra-day is less than 6%, and accuracy of inter-day and intra-day is satisfactory. The method has been applied to the determination of studied drug in pharmaceutical preparations and biological fluids with satisfactory results.

Keywords: Reversed micelle; Ion-pair complex; Chemiluminescence; Flow-injection analysis; Chlorpromazine hydrochloride

1. Introduction

Chlorpromazine (Fig. 1) is one of phenothiazines, which are a group of compounds that are used for the treatment of psychiatric patients suffering from clinical depression. From a bioanalytical and clinical point of view, sensitive and accurate methods are needed to monitor chlorpromazine in pharmaceuticals and biological fluids for quality assurance in preparations and for obtaining optimum therapeutic concentrations. Although many methods have been reported for this purpose [1–6], the selective procedures require relatively extensive sample preparation and are time-consuming, while complicated instruments are used when high sensitivity is desired.

Chemiluminescence (CL) analysis promises high sensitivity with simple instruments (no monochromator required) and rapidity in signal detection (normally 0.1–10 s) compared with other methods. CL reactions have been reported for the determination of chlorpromazine [7–10]. Over the past few years, increasing interest has been given to the use of the reversed micellar system in CL analysis [11–17]. Many advantages including sensitivity and improved selectivity in CL analysis can be achieved by use of the reversed micellar system. The significance of reverse micelles in CL analysis is considered to be due to its unique structure (size/shape) and composition. After dispersion in an apolar organic phase, the molecules of surfactant encompass tiny water droplets and are converted into homogeneously distributed micelles referred to as microreactors. Although not demonstrated, it is believed that reversed micellar mediated CL reactions occur at surfactant–water interfaces [15]. With the additional advantage of sensitivity, these microreactors have the capability to transfer species of experimental interest quantitatively into the water pool [12,13]. The reverse micelles-based CL analysis have been successfully used to trace-level quantification of gold(III) [14,16], rhodium(III)

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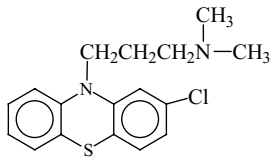

Fig. 1. Molecular structure of chlorpromazine.

[18], iron(III) [13,19], iron(II) [19], vanadium(IV) [20,21] based on the catalytic behavior of different metal ions. Most probably via ion-pair formation in the extraction process, gold(III) was transferred as the tetrachloroaurate ion from aqueous solution into chloroform-containing tri-*n*-octylphosphine oxide [16]. When combined with solvent extraction technique, the reversed micellar mediated CL hybrid method was used to the determination of gold in industrial samples [14,16]. Although numerous papers have been published regarding ion-pair formation between negatively charged metal complexes and protonated analytes [22], the analytical utility of ion-pair formation-based reverse micellar mediated CL has to date received only minor attention [16,17].

There are two tertiary amine groups in chlorpromazine molecular, one in the tricyclic structure and the other adjacent to the aromatic rings. The nitrogen and sulfur atom in the tricyclic structure are easily protonated [23]. Based on above characteristics, in this work, a new CL method for the determination of chlorpromazine is proposed. The method is based on the dichloromethane solvent extraction of ion-pair complex of tetrachloroaurate(III) with protonated chlorpromazine hydrochloride and luminol chemiluminescence detection in a cetyltrimethylammonium bromide reversed micellar medium. The ion-pair complex of tetrachloroaurate(III) with chlorpromazine hydrochloride produced an analytical chemiluminescence signal when it entered the reversed micellar water pool. The proposed method was applied to the determination of chlorpromazine hydrochloride in the commercial preparations and biological fluids with satisfactory results. There are three major differences in analytical methodology as compared to the previous paper by Fujiwara et al. [17] as follows: (1) flow configuration—in Fujiwara's work, the reverse phase flow configuration was adopted, namely, the luminol was injected into the carrier stream. However, in our case, the ion-pair complex of sample with tetrachloroaurate was injected into the carrier stream, which can save the tetrachloroaurate; (2) the method for eliminating the Na^+ interference—according to Fujiwara et al. [17], the possible reason for Na^+ interference behavior was the ion pair between Na^+ and tetrachloroaurate, and Na^+ interference can be eliminated easily by using dichloromethane-to-cyclohexane at a volume ratio of 8 as extracting reagent when performing the atropine analysis. In our experiment, mixture of cyclohexane and *n*-butanol (95:5, V/V) was selected as extractant for the studied drug because it was found that even using dichloromethane as extract reagent, Na^+ interference was still serious. By this way, Na^+ interference can be eliminated and the proposed method can be used to real biological sample; (3) application of the proposed method to real urine sample analysis—as for the analytical application of the method, Fujiwara et al. determined the studied drug (atropine) in synthetic urine samples. However, in our case, we have used the method to determinate the studied drug (chlorpromazine hydrochloride) in real urine samples.

2. Experimental section

2.1. Chemical reagents

All the reagents were of analytical-reagent grade. Luminol was obtained from the Sigma Chemical Co., Inc. (USA). Chlorpromazine hydrochloride was from the Xi'nan Pharmaceutical Company (Chongqing, China). The cetyltrimethylammonium bromide (CTMAB) was obtained from the Aldrich Co., Ltd. (USA). Dichloromethane, cyclohexane, hydrochloric acid and anhydrous sodium carbonate were purchased from Chongqing Chemical Company, Ltd. (Chongqing, China). The chloroauric acid was purchased from the Shanghai First Reagent Factory (Shanghai, China). All chemicals were used as received. Degassed distilled water was used to prepare all aqueous solutions and related cleaning purposes. All glassware was soaked in 10% nitric acid and thoroughly cleaned before use.

2.2. Apparatus

The flow system (Fig. 2) consisted of one peristaltic pump (Longfang Instrument Factory, Wenzhou, China) which delivered a sample stream, carrier stream, and luminescent reagent at a flow rate (per tube) of 3.0 mL min^{-1}; and a glass coil (130 mm, 2 mm i.d.) used as the flow cell, which was placed close to photomultiplier tube of the IFFL-DD Flow-Injection Chemiluminescence Analyzer (Xi'an Reimai Science and Technology Company, Ltd., Xi'an). PTFE tubing (0.8 mm i.d.) was used to connect all components in the

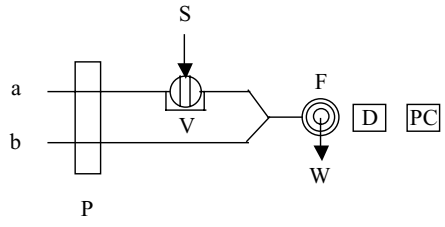

Fig. 2. Schematic diagram of the flow system for the determination of chlorpromazine hydrochloride: (a) cyclohexane; (b) 4×10^{-5} mol/L luminol (in 0.3 mol/L Na_2CO_3 buffer solution with pH of 11.5) dispersed in a dichloromethane–cyclohexane (1:1 V/V) mixture containing 0.125 mol/L CTMAB. S: sample or standard chlorpromazine hydrochloride solution in a dichloroethane; P: peristaltic pump; V: injection valve; F: flow cell; W: waste liquid; D: PMT; PC: personal computer.

flow system. A rotary eight-way injection valve (Longfang Instrument Factory, Wenzhou, China) was used for sample injection. The emitted CL was collected with photomultiplier tube (operated at −450 V) of the IFFL-DD Flow-Injection Chemiluminescence Analyzer. The signal was recorded using an IBM-compatible computer, equipped with a data acquisition interface. Data acquisition and treatment were performed with MEASURE software running under Windows 98.

2.3. Procedure

2.3.1. General procedure

A 1.0×10^{-3} mol/L aqueous stock solution of luminol was prepared in 0.3 mol/L Na_2CO_3 buffer solution with pH of 11.5. A 500 μg/mL chlorpromazine hydrochloride standard stock solution was prepared. More diluted solutions were used immediately after preparation. Certain volume of the luminol solution was dispersed in a dichloromethane–cyclohexane (1:1 V/V) mixture containing 0.125 mol/L CTMAB to prepare luminol reversed micellar solutions. The luminol concentration was 4×10^{-5} mol/L in reversed micellar media. Aqueous standard chlorpromazine hydrochloride solution (10 mL) with the concentration range of 0.05 ∼ 10 μg/mL, containing 400 μg Au(III) as tetrachloroaurate and 0.5 mmol HCl, was placed in a separating funnel, and 4 mL of dichloromethane was added to it. The mixture was shaken vigorously for 5 min and allowed to stand awhile. The lower organic layer was collected in a 5 mL of clean test tube, and diluted to the volume with dichloromethane and was subsequently CL analyzed.

Optimization studies of the analytical conditions were carried out by using the flow-injection system shown schematically in Fig. 2. Sample solution was sucked into the sample loop (160 μL), then was injected into the carrier stream of cyclohexane by using the rotary injection valve, and then merged with the luminescent reagent of reversed micellar luminol solution by means of a T-piece. The carrier and the reagent stream were driven both at a flow rate of 3.0 mL min^{-1}. In a spiral flow cell made of glass mounted in front of photomultiplier tube of the photometer, the luminescent reagent was mixed with ion-pair complex of tetrachloroaurate(III) with chlorpromazine hydrochloride and the CL signal produced was recorded.

2.3.2. Procedure for pharmaceutical preparations

The sugar-coat of chlorpromazine hydrochloride tablets (each with a nominal content of 25 mg of chlorpromazine hydrochloride in tablet) was peeled off firstly. Then at least ten of chlorpromazine hydrochloride tablets free of sugar-coat were weighed to obtain the mean tablet weight, then ground to a homogenized powder; an accurately weighed portion of powder corresponding to 25 mg was then dissolved with 20 mL of doubly distilled water. The resulting mixture was filtered and the filtrate was diluted with doubly distilled water so that the concentration of chlorpromazine hydrochloride was in the working range of the determination of chlorpromazine hydrochloride and the rest of procedures were same as those described above.

Injection samples, each with a nominal content of 25 mg of chlorpromazine hydrochloride in 1 mL, were diluted to 100 mL with doubly distilled water and further diluted to the working range of the determination of chlorpromazine hydrochloride. Proceed as described above.

2.3.3. Procedure for real urine samples

Take 10 mL of urine sample from the psychiatric patients suffering from clinical depression in the local hospital into a tube, and then add certain amount of ammonium hydroxide and 10 mL of cyclohexane-*n*-butanol (95:5, V/V), respectively. After shaking for 1 min, the tube was allowed to stand awhile. The organic layer was collected in a clean test tube, then certain amount of 0.06 mol/L HCl was added to back-extract the studied drug. The aqueous phase was collected in a clean test tube, and tetrachloroaurate was added to get concentration of 40 mg/L. Finally, 5 mL of dichloromethane was used to extract the ion-pair complex of tetrachloroaurate(III) with chlorpromazine hydrochloride and was subsequently CL analyzed. A blank value was determined by treating the distilled water in the same way.

3. Results and discussion

The principle for the determination of chlorpromazine hydrochloride is based on chemiluminescence signal produced by ion-pair complex of tetrachloroaurate(III) with studied drug in the reversed micellar water pool containing luminol. In order to study the role of tetrachloroaurate(III), the chemiluminescence signals versus concentrations of tetrachloroaurate(III) without and with chlorpromazine hydrochloride were studied. It was found that in the absence of studied drug, weak signals were obtained, whereas very strong signals were obtained in the presence of studied drug (Fig. 3). This demonstrates that tetrachloroaurate(III) was a counter ion of chlorpromazine for the ion-pair extraction and an catalysis of the CL. The ion-pair complex of tetrachloroaurate(III) with studied drug disassociates when it entered the reversed micellar water pool, then the free tetrachloroaurate react with luminol producing CL signals. The more the studied drug added, the more the tetrachloroaurate disassociated in the reversed micellar water pool.

3.1. Effect of the tetrachloroaurate concentration

The effect of the tetrachloroaurate concentration on the CL response was shown in Fig. 3. As can be seen that in the absence of tetrachloroaurate, there is no CL signals produced. When tetrachloroaurate concentration increased, the

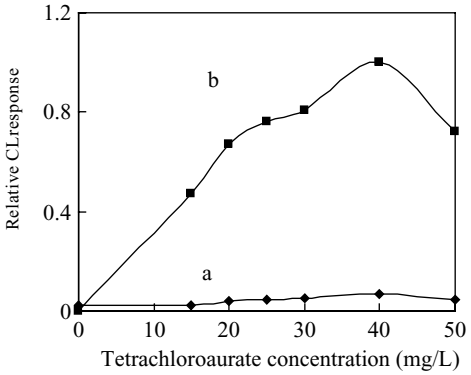

Fig. 3. Effect of tetrachloroaurate concentration on CL intensity: (a) sample-free blank CL signal; (b) sample CL signal. Concentration of chlorpromazine hydrochloride: 1.25 μg/mL.

CL intensity increased. However, the blank CL signal also increased (Fig. 3a) because tetrachloroaurate in an acidic medium is also slightly extractable in the form of chloroauric acid [16]. Therefore, an aqueous tetrachloroaurate solution without chlorpromazine hydrochloride was used to prepare the blank and extracted with dichloromethane, and finally used to determine a blank signal. An analytical CL signal was taken as the difference in observed peak heights for the analyte and the blank. As shown in Fig. 3, CL intensity increases with the concentration of tetrachloroaurate up to 40 mg/L, thereafter decreased. Therefore, 40 mg/L of tetrachloroaurate was selected for the present study.

3.2. Effect of hydrochloric acid concentration

The method for the determination of chlorpromazine hydrochloride proposed in this work is based on the formation of ion-pair complex between negatively charged tetrachloroaurate(III) with positively protonated chlorpromazine hydrochloride, therefore, the effect of HCl concentration on the CL response was investigated. It was found that CL was hardly observed in the absence of HCl, suggesting the absence of protonated chlorpromazine hydrochloride. When HCl concentration increases, the sulfur and nitrogen atom in the tricyclic structure of chlorpromazine is protonated in an acidic medium and is then associated with a negatively charged counter ion containing tetrachloroaurate. Once ion-pair complex formed, it is then quickly and efficiently extracted into a slightly polar solvent such as dichloromethane. CL intensity increases with the concentration of HCl up to 0.05 mol/L, thereafter, CL intensity decreases slowly probably due to a small quantity of free HCl which was accumulated in dichloromethane during the extraction process, ultimately causing an alteration in the constitution of the luminol buffer in the reversed micellar water pool [17]. Finally, a 0.05 mol/L concentration of HCl was selected to be the optimum for facilitating both protonation and ion-pair formation.

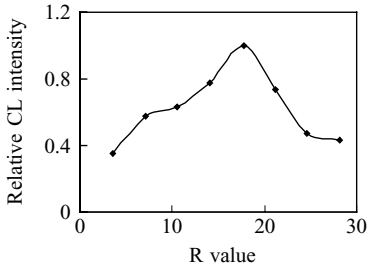

Fig. 4. Dependence of the CL intensity on the R ([H_2O]/[CTMAB]) value, [CTMAB] = 0.125 mol/L. Concentration of chlorpromazine hydrochloride: 1.25 μg/mL.

3.3. Effect of the [H_2O]/[CTMAB] molar ratio

In general, the molar ratio of the [H_2O]/[CTMAB], R, strongly affects the physiochemical properties of the reverse micelles. The size of the reverse micelles is controlled by R value [24]. The R value can be changed by varying either the amount of water or the concentration of the surfactant in the micellar medium. The R value increases as the CTMAB concentration is lowered at a constant amount water in the reversed micellar system. The effect of the [H_2O]/[CTMAB] molar ratio, R, on the relative CL intensity was studied at different R value. As illustrated in Fig. 4, at a constant CTMAB concentration of 0.125 mol/L in the micellar medium, CL intensity increases with the increase of R value up to 17.8; above which the CL intensity decreased. An optimum R value of 17.8 was selected and was further investigated by changing the amount of surfactant and keeping the amount of water constant. Both results for the CL signals agreed for the corresponding values of R. An increase in the R value (hence more free water was available for CL reaction) caused an increase in the size of the reverse micelles [25]. At a constant R value of 17.8, the CL intensity increased upon an increase in both the CTMAB concentration and the amount of water in the reversed micellar solution. Upon changing the amount of water and the surfactant concentration at a fixed R, the sizes of the reverse micelles remain unchanged, but their population is increased. Therefore, it is supposed that an increase in the surfactant concentration and amount of water in the reverse micelles at a constant value of R leads to the formation of more micelles or microreactors of identical size. CL signals of maximum intensity were observed around a CTMAB concentration of 0.125 mol/L, which was selected as the optimum concentration for the surfactant in the present study.

3.4. Effect of the luminol concentration

The concentration effect of luminol upon the CL behavior of studied drug in reversed micellar solution was examined over the range $4\times10^{-8} \sim 2\times10^{-4}$ mol/L. The maximum emission intensity was obtained at 4×10^{-5} mol/L luminol. So, 4×10^{-5} mol/L luminol was adopted as the optimum luminol concentration in present experiment.

Table 1
Accuracy and precision data at three concentrations

Concentration (μg/mL)	Inter-day[a]			Intra-day[a]		
Added	Found	Error (%)	R.S.D. (%)	Found	Error (%)	R.S.D. (%)
0.1	0.096	−4.0	5.8	0.098	−2.0	4.7
1	0.959	−4.1	3.5	1.005	0.5	2.0
5	5.175	3.5	3.0	5.104	2.1	1.6

Determinations of precision and accuracy were performed between five days and five times in one day for intra-day and inter-day, respectively.
[a] Averages of five determinations.

3.5. Effect of the sodium carbonate concentration

Due to the nature of the luminol reaction, which is more favored in basic conditions. Therefore, sodium carbonate solution was added in a flow line to improve the sensitivity of reaction. The results show that 0.3 mol/L sodium carbonate buffer solution with pH value of 11.5 was found to give the highest CL intensity. Therefore, 0.3 mol/L sodium carbonate buffer solution with pH value of 11.5 was selected for the present work.

3.6. Analytical performance

Under the optimized conditions given above, the calibration graph of emission intensity vs. chlorpromazine hydrochloride concentration is linear in the range from 0.05 to 10 μg/mL ($\Delta I = 667.19$ [chlorpromazine hydrochloride] (μg/mL) + 674; $r = 0.99$, $n = 8$). The detection limit (DL) for chlorpromazine hydrochloride was 6 ng/mL, where the DL is given as the concentration for which the analytical signal is three times higher than standard deviation of blank intensity. The relative standard deviation was 2.6% for 1.25 μg/mL chlorpromazine hydrochloride ($n = 11$). Three replicate determinations at three concentration levels were carried out to test the accuracy and precision of the proposed method and the results listed in Table 1. As can be seen, R.S.D. (precision) of inter-day and intra-day is less than 6%, and accuracy of inter-day and intra-day is satisfactory.

3.7. Interference study

The effect of foreign substances was tested by analyzing a standard solution of chlorpromazine hydrochloride (1.25 μg/mL) to which increasing amounts of interfering substances were added. The tolerable concentration ratios with respect to 1.25 μg/mL chlorpromazine hydrochloride for interference at 5% level were over 1000 for Co^{2+}, Mn^{2+}, Cr^{3+}, Hg^{2+}, Ca^{2+}, Zn^{2+}, Mg^{2+}, K^+, NH_4^+, HCO_3^-, Pb^{2+}, HSO_3^-, CO_3^{2-}, urea, maltose, glucose; 650 for amylus; 500 for dextrin; 400 for SO_4^{2-}; 100 for Fe^{3+}; 50 for Na^+; 10 for ascorbic acid; respectively. The results show that the proposed method has good selectivity for chlorpromazine hydrochloride determination. However, Na^+ shows a high interference. According to Fujiwara et al. [17], the possible reason for Na^+ behavior was the ion pair between Na^+ and tetrachloroaurate, and Na^+ interference can be eliminated easily by using CH_2Cl_2-cyclohexane at a volume ratio of above 8 as extracting reagent when performing the atropine analysis. In the case of chlorpromazine, however, even using CH_2Cl_2 as extract reagent, Na^+ interference was serious. In order to eliminate Na^+ interference, cyclohexane-*n*-butanol (95:5, V/V) was selected as extractant for the studied drug in the basic media. After extraction, the studied drug was back-extracted using aqueous HCl. Bay this way, Na^+ interference can be eliminated and the proposed method can be used to real biological sample.

3.8. Application of the method

3.8.1. Analysis of pharmaceutical preparations

Following the procedure detailed under Section 2, the proposed method was applied to the determination of chlorpromazine hydrochloride in tablets. The results are listed in Table 2. The chlorpromazine hydrochloride concentrations agree well with those obtained by UV spectrophotometry. The UV spectrophotometric determination of chlorpromazine hydrochloride was performed according to the literature [23].

3.8.2. Analysis of real urine samples

The comparison of detection limit with other CL-based method or UV spectrophotometric suggests high sensitivity of the proposed method for chlorpromazine hydrochloride. As stated above, the proposed method gave a detection limit of 6 ng/mL for chlorpromazine hydrochloride, which is lower than those given by other methods. For example, Basavaiah et al. [26] reported a DL of 27 ng/mL

Table 2
Results of the determination of chlorpromazine hydrochloride in tablets and injections

Sample	Labeled	Found (mg or mg/mL) ± R.S.D. (%)[a]	
		Proposed method	UV spectrophotometry
Tablet 1	25 mg	25.2 ± 0.40	22.2 ± 0.32
Tablet 2	25 mg	25.0 ± 0.80	21.6 ± 0.26
Tablet 3	25 mg	25.2 ± 0.20	23.5 ± 0.48
Injection 1	25 mg/mL	24.9 ± 0.30	24.7 ± 0.72
Injection 2	25 mg/mL	24.9 ± 0.42	24.5 ± 0.68
Injection 3	25 mg/mL	24.8 ± 0.52	24.5 ± 0.50

[a] Average of five measurements.

Table 3
Results of the determination of chlorpromazine hydrochloride in urine samples

Urine sample number	Proposed method (μg/mL) ± R.S.D. (%)[a]	UV spectrophotometry (μg/mL) ± R.S.D. (%)[a]
1	0.095(2.83)	0.091(3.62)
2	0.050(2.52)	0.049(3.14)
3	0.094(1.64)	0.092(2.22)

[a] Average of three measurements.

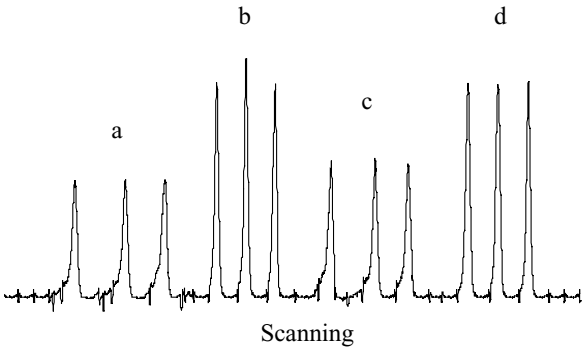

Fig. 5. A typical FIA chart from three real urine samples: (a) blank; (b) no. 1 urine sample; (c) no. 2 urine sample; (d) no. 3 urine sample.

by UV spectrophotometry. When using the hydrogen peroxide-bis(2,4,6-trichlorphenyl)oxalate chemiluminescence system [7] and tris(2,2′-bipyridy)ruthenium(II)-based electrogenerated chemiluminescence system [10], 66.5 and 240 ng/mL of DL were reported; respectively. So, the high sensitivity of the proposed method allows the determination of chlorpromazine hydrochloride in biological fluids. Table 3 shows the results of chlorpromazine hydrochloride determination in urine samples from the psychiatric patients suffering from clinical depression. The typical FIA chart from urine samples were given in the Fig. 5. As can be seen, the high sensitivity of the proposed method allows the determination of chlorpromazine hydrochloride in urine samples with satisfactory results, and the results obtained by the proposed method are consistent with those by UV spectrophotometry [23].

Table 4
Results of the determination of chlorpromazine hydrochloride in spiked urine

Concentration added (μg/mL)	Recovered (%), R.S.D. (%), $n = 3$
0.05	99.24(0.12)
0.1	98.63(2.78)
0.2	95.29(2.57)
0.3	104.4(0.99)
0.4	102.4(0.81)
0.5	98.27(0.72)
1	96.34(0.94)
2	101.3(1.35)
3	98.86(0.58)
4	102.3(0.56)
5	99.28(0.73)
10	95.36(0.98)

The major urinary metabolite of chlorpromazine is chlorpromazine sulfoxide [27]. Formation of sulfoxide decreases the potential of prontonation as compared with the parent compound. The recovery test on the spiked urine samples at different concentration levels demonstrates good results (shown in Table 4). So, the effect of the urinary metabolites of chlorpromazine on the chemiluminescence signal is minor. Results obtained by the UV spectrometry demonstrates that the metabolite of chlorpromazine hydrochloride did not affect its determination.

4. Conclusions

Chlorpromazine can be protonated under acidic conditions. The protonated chlorpromazine is then associated with a negatively charged tetrachloroaurate(III) and form the ion-pair complex which can be quickly and efficiently extracted into a slightly polar solvent such as dichloromethane. The ion-pair complex of tetrachloroaurate(III) with chlorpromazine hydrochloride produced an analytical chemiluminescence signal when it entered the cetyltrimethylammonium bromide reversed micellar water pool. The proposed method has been applied to the determination of chlorpromazine hydrochloride in the commercial preparations and biological fluids with satisfactory results.

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