A diperiodatoargentate(III)-based chemiluminescence determination of mitoxantrone in pharmaceutical preparations and human serum

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ABSTRACT
Chemiluminescence (CL) method, combined with the flow-injection (FI) technique, is an attractive alternative for pharmaceutical analysis. In this paper, a CL reaction between diperiodatoargentate (III) (DPA) and mitoxantrone (MTX) was observed. A strong CL signal was generated during the reaction of mitoxantrone with DPA in an alkaline medium. Thus a highly sensitive flow injection CL method was developed for the determination of mitoxantrone. Optimized experimental conditions were investigated in detail. Under the optimum conditions, the relative CL intensity was linear with the mitoxantrone concentration in the range of $8.0\times10^{-10}$–$5.0\times10^{-7}$ g/mL with a correlation coefficient of 0.9994 and the detection limit was $1.9\times10^{-10}$ g/mL. The proposed method had good reproducibility with a relative standard deviation of 1.5% ($n=11$) for $1.0\times10^{-7}$ g/mL mitoxantrone. The highly sensitive method was successfully applied to the determination of mitoxantrone in pharmaceutical preparation and serum samples with satisfactory results. The possible CL reaction mechanism was also discussed briefly.

1. Introduction
Antibiotic, a type of antimicrobial drug, is usually used in the treatment and prevention of bacterial infections within a limited concentration range (1). However, the uncontrolled/incorrected use of antibiotics led to its accumulation in animal-derived products, long-term intake might cause serious side effects, e.g. antibiotic resistance, allergic reaction and nephrotoxicity (2). Accordingly, accurate quantification, instant analysis, and cost-efficient detection of antibiotics and antibiotic residue are of critical significance. Up to now, numerous approaches for the determination of antibiotics have been reported, e.g. high performance liquid chromatography (3), colorimetric assays (2, 4), electrochemical methods (5, 6), bioassay (7–9), and fluorescence measurement (10, 11).

Mitoxantrone, chemically known as 1,4-dihydroxy-5,8-bis[(2-hydroxyethyl) amino] ethyl amino]-9,10-anthraquinone (MTX, Figure 1) is an anthracycline antibiotic, which shows high therapeutic effect in the treatment of acute non-lymphocytic leukemia, prostatic carcinoma, malignant lymphoma, breast cancer and so on (12–14). Although it has a few side effects, they can occur with all medications and the serious side effects that have been reported with mitoxantrone were cardio toxicity, myelosuppression, and secondary myeloid leukemia. It was important to monitor the...
concentration level of mitoxantrone in plasma during the process of therapeutic and toxic control. Therefore, the development of simple, sensitive, and precise method for industrial quality control and clinical monitoring of mitoxantrone is essential.

Several analytical methods have been proposed for the determination of mitoxantrone in pharmaceutical formulations and biological fluids, including electrochemical (15), high performance liquid chromatography (HPLC) (16), fluorescence (17, 18), capillary electrophoresis (CE) (19), and chemiluminescence (CL) (20). However, these assay methods suffered from the drawbacks of expensive instrumental, low sensitivity, time-consuming, and low sample throughput. The CL method (20), based on the enhancement of the tris-(4,7-diphenyl-1,10-phenanthroline)disulfonic acid) ruthenium (II)-cerium (IV) system, has a detection limit of $6.2 \times 10^{-9}$ g/mL and a narrow linear range. The goal of the present work was to develop a rapid, simple and sensitive method for the determination of mitoxantrone in pharmaceutical preparations and serum samples.

In the recent past, some transition metals in the highest oxidation states, such as trivalent silver, have widened the application of CL analysis. Diperiodatoargentate (DPA) is a powerful oxidizing agent in a medium with an appropriate pH value, which has a reduction potential of 1.74 V (21). DPA is a strong versatile nature of the two electron oxidants for the oxidation of various organic compounds in the alkaline medium (22). Because the structure of this complex is considered as $\text{[Ag(H}_2\text{IO}_6\text{)]}^-$ in the alkaline medium, which has a square-planar coordination geometry around the metal center, so that this complex is fairly stable in the alkaline medium (23). Although there are a considerable amount of research studies concerning the use of DPA as an oxidant in the alkaline medium, reports about the use of DPA direct oxidation in CL analysis are relatively few. Yang et al. (24) developed a CL system for the determination of uric acid by using DPA direct oxidation uric acid in the alkaline medium. Asghar et al. (25) reported an analysis method for the determination of cyromazine in natural water samples based on the reaction of cyromazine with DPA in a sulfuric acid medium sensitized by DPA.

CL method combined with flow-injection (FI) technique, is an attractive alternative for pharmaceutical analysis (26). To the best of our knowledge, there was no report using DPA for mitoxantrone analysis by CL method. In this paper, it was found that strong CL was produced after mitoxantrone mixed with DPA in the alkaline medium. The relative CL intensity was proportional to the concentration of mitoxantrone. Based on this observation, a simple enhanced FI-CL assay for the rapid and sensitive determination of mitoxantrone has been developed. The result of the related studies showed that the proposed method offers a high...
sensitivity and good accuracy, which has been successfully applied to the determination of mitoxantrone in pharmaceutical preparations and biological fluid. And the possible mechanism has also been discussed on the basis of CL spectra and UV spectra.

2. Experimental

2.1. Reagents

All solutions were prepared from analytical reagent-grade materials, and ultra-pure water was used.

Figure 4. Kinetic CL intensity-time profile in the static system. (1) CL intensity in the absence of mitoxantrone; (2) CL intensity in the presence of mitoxantrone. Conditions: DPA, $1.0 \times 10^{-4}$ mol/L (0.1 mol/L KOH); MTX, $3.0 \times 10^{-9}$ g/mL.

Figure 5. Effect of KOH, DPA concentration and flow rate on the relative CL intensity for $1.0 \times 10^{-7}$ g/mL MTX. Conditions: (a) DPA, $8.0 \times 10^{-5}$ mol/L; flow rate, 2.3 mL/min. (b) KOH, 0.05 mol/L; flow rate, 2.3 mL/min. (c) KOH, 0.05 mol/L; DPA, $8 \times 10^{-5}$ mol/L.
throughout. Sodium periodate (NaIO₄), sodium nitrate (NaNO₃), and potassium hydroxide (KOH) were obtained from Kermel Chemical Reagent Company (Tianjin, China). Potassium peroxydisulfate (K₂S₂O₈) was purchased from Sinopharm Chemical Reagent Co., Ltd. (Beijing, China). Silver nitrate was from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). Mitoxantrone was obtained from Yikangsida Medical Science and Technology Company (Beijing, China).

Mitoxantrone stock solution (1.0 × 10⁻⁴ g/mL) was prepared by dissolving 10.03 mg mitoxantrone with ultra-pure water to 100 mL in a brown volumetric flask to avoid exposure to light and stored in the refrigeration at 4°C. More working solution was prepared by serial dilution with ultra-pure water as required.

### 2.2. Apparatus

CL measurements were carried out on a computerized ultra-weak luminescence analyzer (IFFM-E, Remax Analytical Instrument Limited Co. Ltd, Xi’an, China), the schematic diagram is shown in Figure 2. Two peristaltic pumps were used to deliver flow streams in this system. Polytrafluoroethylene flow tubes (0.8 mm i.d.) were used to connect all the components throughout. The flow cell was made by coiling 10 cm of colorless glass tube (0.5 mm i.d.) and the distance between injection valve and flow cell was about 10 cm. The CL signal was monitored by the photomultiplier tube (PMT) voltage of 800 V placed near the flow cell and was recorded with a computer. A UV-visible spectrophotometer (Model UV-2550, Shimadzu, Japan), with 1.0 cm light path length-matched quartz cells, was used for absorbance measurements. The chemiluminescence spectrum was monitored with a RF-5301 fluorescence spectrophotometer (Shimadzu, Japan) to study the luminescence characteristics.

### 2.3. Procedures

#### 2.3.1. Synthesis of DPA

DPA was synthesized using the method suggested by Zhao (27). In brief, AgNO₃ (1.36 g), NaIO₄ (3.42 g), K₂S₂O₈ (3.00 g), and KOH (8.00 g) were added to 100 mL water in a 250 mL round bottomed flask. The mixture was heated to boiling for about 15 min on a hot plate with constant stirring. The boiling mixture turned orangish-yellow and the boiling was continued for another 15 min. The mixture was then cooled to room temperature and filtered with a filter paper. The product solution was cooled in an iced bath to eliminate as much of potassium sulfate as possible and the solution filtered again while cold. The resulting orangish-red clear filtrate was left to reach room temperature. To isolate the complex, 40 mL of NaNO₃ solution (50%, in excess) was added to the solution and the mixture left to crystallize. The crystals were filtered and washed several times with ultra-pure water until the complex starts dissolving, which was indicated by the orange–red drops being formed under the funnel. The DPA solutions were freshly prepared by dissolving the amount of the complex in 0.01 mol/L KOH solutions before experiment. The complex was characterized by the UV-visible spectrum, which showed two absorption maxima at 360 nm and 252 nm (Figure 3). The concentration of DPA solution was determined by the absorbance at 360 nm with a molar absorptivity (ε) of 1.26 × 10⁴ mol⁻¹ L cm⁻¹.

#### 2.3.2. Flow-injection chemiluminescence method

To obtain mechanical and thermal stability, the instruments were run for at least 10 min before the first

### Table 1. Comparison of the reported CL methods and the proposed method for the determination of mitoxantrone.

| CL system                        | Linear range (g/mL) | Detection limit (g/mL) | Application                                      | Reference |
|----------------------------------|---------------------|------------------------|--------------------------------------------------|-----------|
| K₂Fe(CN)₆-luminol                | 3.1 × 10⁻⁸–4.4 × 10⁻⁶ | 4.4 × 10⁻⁹             | Pharmaceutical preparations and serum samples     | (19)      |
| Tris-(4,7-diphenyl-1,10-phenanthrolinedisulfonic acid) ruthenium(II) -cerium (IV) | 1.8 × 10⁻⁸–3.8 × 10⁻⁶ | 6.2 × 10⁻⁹             | Pharmaceutical preparations and serum sample      | (20)      |
| KMnO₄ -HCHO                      | 1.0 × 10⁻⁸–1.0 × 10⁻⁶ | 6.4 × 10⁻⁹             | Pharmaceutical preparations                      | (28)      |
| DPC -luminol                     | 5.0 × 10⁻⁹–1.0 × 10⁻⁷ | 1.1 × 10⁻⁹             | Pharmaceutical preparations and serum samples     | (29)      |
| DPA -mitoxantrone                | 8.0 × 10⁻¹⁰–5.0 × 10⁻⁷ | 1.9 × 10⁻¹⁰            | Pharmaceutical preparations and serum samples     | This work |

### Table 2. Tolerable concentration ratios of interferents in the analysis of 8.0 × 10⁻⁸ g/mL mitoxantrone.

| Substance | Tolerance concentration ratio (C_{species}/C_{MTX}) |
|-----------|---------------------------------------------------|
| ctDNA, K⁺, Cl⁻ | 1000                                              |
| NH₄⁺, CO₃²⁻ | 500                                               |
| Mannitol   | 300                                               |
| Sodium citrate | 200                                                |
| Mg²⁺, Al³⁺, Lactose, Na⁺, NO₃⁻, EDTA | 100                                               |
| L-Serine, Ca²⁺ | 50                                                 |
| Cu²⁺, hsDNA, Vc, Glucose | 10                                                 |
| Fe³⁺, β-CD, Tryptophan | 5                                                  |

This work
measurement. As shown in Figure 2, the mitoxantrone was injected into the KOH solution by a six-way injection valve, which was then merged with the stream of DPA solution. The mixed solution was delivered to the flow cell, producing CL emission. The CL signals generated from the flow cell were detected and amplified by PMT and a luminometer, whose output was connected to the data processing system for data acquisition. The concentration of mitoxantrone was quantified by measuring the relative CL intensity \( \Delta I = I_s - I_o \), where \( I_s \) was the CL intensity of sample solution, and \( I_o \) was the blank solution.

### 2.3.3. Sample preparation

The human serum samples were supplied by the Red Cross Blood Centre in Henan Province (China). Three different amounts of solutions of mitoxantrone were introduced into a 200 μL serum ultra-filtration tubes. After mixing for 3 min, these mixtures were centrifuged at 10,000 rpm for 20 min. Then the supernatant was appropriately diluted with the water. A blank solution was prepared in the same way.

### 3. Results and discussion

#### 3.1. Kinetic characteristics of the CL reaction

The kinetic profile of the CL reaction plays an important role in the design of the CL flow system. The CL intensity-time curve is shown in Figure 4; the results indicated that mixing of DPA with KOH solution generated a weak CL signal (curve 1). After the addition of mitoxantrone into the DPA-KOH system, a strong enhancement on CL signal was observed within 2.5 s (curve 2). It took about 16 s from reaching the peak maximum to declining to the baseline level.

#### 3.2. Optimization of experimental conditions

A series of univariate search studies were optimized analytically conditions. The main parameters optimized were KOH, DPA concentrations, and flow rate. All these experiments were performed with a 1.0 × 10⁻⁷ g/mL mitoxantrone standard solution and a PMT voltage of 800 V.

The CL reaction occurred in alkaline condition and the effect of KOH concentration on the CL intensity was studied from 0.005 to 1.0 mol/L. As shown in Figure 5(a), when 0.05 mol/L KOH solution was used, the CL reaction had the maximum CL intensity.

In the CL system, DPA can be used as an oxidant in the aqueous alkaline medium. The effect of DPA concentration was examined over the range of 8.0 × 10⁻⁶–5.0 × 10⁻⁴ mol/L, as demonstrated in Figure 5(b). The results showed that the maximum relative CL intensity and stability was obtained with 8.0 × 10⁻⁵ mol/L DPA. Thus, 8.0 × 10⁻⁵ mol/L of DPA was chosen for further studies.

The flow rate is an important factor that influences the analytical sensitivity. The effect of the flow rate of two pumps on CL intensity was examined in the range of 1.2–3.7 mL/min. The results showed that the CL signal increased with the increasing of flow rate (Figure 5(c)), but a high flow rate might lead to the irreproducibility and waste of reagents. Finally, the flow rate of 2.3 mL/min was selected as optimum.

#### 3.3. Analytical characteristics

Under the optimized experimental conditions shown above, the calibration curve of the relative CL intensity (\( \Delta I \)) versus mitoxantrone concentration was linear in the range of 8.0 × 10⁻¹⁰–5.0 × 10⁻⁷ g/mL with a detection limit of 1.9 × 10⁻¹⁰ g/mL. The regression equation was \( \Delta I = 3601.4C – 144.71 \) (\( C \), 10⁻⁷ g/mL) with a correlation coefficient of 0.9994. The relative standard deviation (RSD) was 1.5% for 11 replicate determinations of 1.0 × 10⁻⁷ g/mL mitoxantrone.

As an oxidant reagent, the uses of DPA direct oxidation mitoxantrone made the reaction simple and avoided being interfered by other substances. In comparison with other CL methods (19, 20, 28, 29) reported

| Table 3. Recovery rate of externally added mitoxantrone in pharmaceutical preparations. |
|----------------|----------------|----------------|---------------|----------------|----------------|
| Sample        | Labeled (%)   | Fi-CL method concentrationa | Added concentration (%) | Found concentration (%) | Recovery Rate (%) |
| No.            | (×10⁻² g/mL)  | (×10⁻⁴ g/mL)                | (×10⁻⁵ g/mL)             | (×10⁻⁵ g/mL)            | (RSD, %, n = 3)  |
| 1              | 3.00          | 2.90 ± 0.02                 | 1.00                      | 3.83                      | 93.0 (1.05)      |
| 2              | 6.00          | 5.94                        | 6.00                      | 8.59                      | 94.8 (0.86)      |
| 2              | 3.00          | 3.87                        | 3.00                      | 5.83                      | 97.0 (1.24)      |
| 3              | 6.00          | 8.75                        | 6.00                      | 8.59                      | 97.2 (2.19)      |

aMean ± SD of three measurements.

| Table 4. Recovery for mitoxantrone in human serum samples. |
|----------------|----------------|----------------|---------------|----------------|----------------|
| Sample no.     | Added (%)      | Detected (%)   | Recovery (%)  | RSD (%)        |
| 1              | 1.00           | 1.06           | 106.3         | 1.56           |
| 2              | 5.00           | 4.68           | 93.6          | 0.98           |
| 3              | 10.00          | 9.56           | 95.6          | 2.35           |
for the determination of mitoxantrone, as shown in Table 1, the proposed method displays higher sensitivity and a wider linear range.

Because mitoxantrone is an anthracycline antibiotic, we should pay attention to a series of problems caused by antibiotic residues. The most intuitive effect on human health is that pathogens become resistant to the antibiotics used, which then make the disease refractory to standard treatments (30–32). Therefore, sensitive monitoring of antibiotic concentration is helpful to avoid superfluous use of antibiotics and production of antibiotic residues.

3.4. Interference

To assess the applicability of the developed method, the effect of some common compounds usually presents in pharmaceutical preparations, some metal ions and coexisting species in human serum were investigated under the optimized conditions by testing $8.0 \times 10^{-8}$ g/mL mitoxantrone. The tolerable limit of a foreign species was taken as a relative error less than $\pm 5\%$ variation of CL peak height: $(I_{\text{species}} - I_{\text{MTX}})/I_{\text{MTX}}$. The tolerable ratio for foreign species is listed in Table 2. It can be seen that most common inorganic ions and organic substances have almost no effect on the determination of high concentration of mitoxantrone.

3.5. Analytical application

3.5.1. Determination of mitoxantrone in injections

To investigate the applicability and precision of the developed method, recovery tests were performed by adding known amounts of mitoxantrone in the injection samples according to the proposed method. Three different batch numbers mitoxantrone injections (Sichuan Shenghe Chemical Co., Ltd., China) were dissolved in ultra-pure water. Working solutions were prepared by appropriate dilution with ultra-pure water prior to the measurement so that the final analytic concentrations were in the linear response range. As the results listed in Table 3, the recovery of mitoxantrone

![Figure 6. UV-vis absorption spectra. (1) DPA; (2) MTX; (3) DPA + MTX. conditions: DPA, $2.7 \times 10^{-5}$ mol/L (KOH 0.05 mol/L); MTX, $1.0 \times 10^{-5}$ g/mL.](image1)

![Figure 7. CL spectra of the proposed system. conditions: DPA, $8.0 \times 10^{-4}$ mol/L (KOH 0.2 mol/L); MTX, $3.3 \times 10^{-5}$ g/mL.](image2)
in injections samples was in the range of 93.0–101.3%, suggesting that the proposed method for the determination of mitoxantrone in injections samples was acceptable.

### 3.5.2. Determination of spiked serum samples

Following the procedure described under Section 2.3.3, the proposed method was utilized for the determination of mitoxantrone in human serum samples. The standard addition method was applied to the recovery test to evaluate the accuracy feasibility of the method. The results of recovery in human serum are shown in Table 4. The recoveries for human serum samples are 93.6–106.3%, suggesting that the developed method was acceptable.

### 4. Possible mechanism

To explore the possible mechanism of this CL enhancing phenomena, the following experiments were performed. Firstly, the UV-vis absorption spectra of DPA, mitoxantrone and DPA-mitoxantrone were measured (Figure 6). As shown in Figure 6(1), two absorption peaks were observed at about 252 nm and 360 nm for DPA in alkaline solution. From Figure 6(2), mitoxantrone has two characteristic absorption peaks at 611 nm and 662 nm. As can be seen from Figure 6(3) when DPA and mitoxantrone were mixed in the alkaline medium, the characteristic absorption peaks of DPA and mitoxantrone almost disappear except for the peak at 650 nm. In addition, the color of DPA and mitoxantrone faded. However, when a strong oxidant (K₂S₂O₈) was added into this near colorless solution, the primary color of DPA recovered. Therefore, it is suggested that a redox reaction took place between mitoxantrone and DPA in the alkaline medium.

For getting a better idea about the nature of the CL reaction, the CL spectra of the reaction of DPA and mitoxantrone were examined by using an RF-5301 model spectrofluorometer, as shown in Figure 7. It was observed that there was one broad band with a maximum at 490 nm when DPA mixed with mitoxantrone in the alkaline medium.

**Figure 4** shows that in the presence of mitoxantrone, CL intensity of DPA in the alkaline medium was enhanced. **Figure 6** shows the absorption peak of mitoxantrone in the presence of DPA moved from 611 nm and 662 nm to 650 nm. This suggested that DPA and mitoxantrone formed a complex, resulting in an enhancement effect to CL emission.

According to the previous study (27, 33, 34), we consider that [Ag(HIO₄)(OH)(H₂O)]²⁻ (Ag(III)*) is the active center of DPA in the alkaline medium. The CL mechanism is described as follows: The hydroxide ions existing in the alkaline medium deprotonate DPA, and active center Ag(III)* for DPA could oxidize mitoxantrone to produce an intermediate complex. In addition, active center Ag(III)* with dissolved oxygen in the solution could produce superoxide anion radical (‘O₂⁻). The recombination of part of ‘O₂⁻ may generate energy-rich precursors of excited molecules (O₂)₂* (33, 34). The CL emission produced from the DPA-MTX system is suggested via the intermolecular energy transfer from (O₂)₂* to a complex of Ag(III)* and mitoxantrone, then the excited complex returned to its ground state, producing the CL emission. Based on the above discussions, the possible mechanism for the enhanced effect of mitoxantrone on CL emission of DPA for the system can be proposed in Scheme 1.

### 5. Conclusion

In the present study, the use of DPA for direct determination of mitoxantrone in the alkaline medium was developed. The method has been proposed to determine the concentration of mitoxantrone based on CL reaction of DPA and mitoxantrone. The method proved to be an attractive analytical method owing to its simplicity, high sensitivity, rapidity, and wide linear rang. The method also has been successfully applied to the measurement of drugs in pharmaceutical and biological samples.
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Disclosure statement

There are no conflicts to declare.

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