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Flow injection chemiluminescence determination of isoxicam based on diperiodatoargentate(III)-fluorescein system in a micellar medium

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ABSTRACT

A novel and highly sensitive flow injection chemiluminescence (FI-CL) method has been developed for the assay of isoxicam. The method is based on the luminescence of the diperiodatoargentate(III)-fluorescein-isoxicam system, where fluorescein is used as an energy-transfer reagent in alkaline medium. The emission intensity is greatly enhanced by the presence of cetyltrimethylammonium bromide (CTAB). Optimum conditions and possible mechanisms have been investigated. The relative CL intensity is linear with the isoxicam concentration in the range of 3.0×10^{-10}–1.0×10^{-6} g/ml with a detection limit of 7.0×10^{-11} g/ml (3σ). The relative standard deviation (RSD) is 1.7% at 1.0×10^{-8} g/ml of isoxicam ($n=11$). The present CL procedure was successfully applied to the determination of isoxicam in pharmaceutical formulations and biological fluids.

1. Introduction

Isoxicam, chemically known as 4-hydroxy-2-methyl-N-5-methyl-3-isoxolyl-2H-1, 2-benzothiazine-3-carboxamide-1, 1-dioxide (Fig. 1), is a potent long acting anti-inflammatory agent from the oxicam group, highly effective in relieving the symptoms of rheumatoid arthritis and degenerative joint disease. The therapeutic effect of isoxicam is the result of its ability to inhibit prostaglandin synthesis via inhibition of cyclooxygenase and subsequent prostaglandin formation [1]. Side effects can occur with all medications, and the most important side effects that have been reported with isoxicam are hepatic toxicity and skin toxicity [2]. The importance of sensing isoxicam might benefit for elder homecare system especially Stevens-Johnson syndrome or toxic epidermal necrolysis [3,4]. Therefore, the development of simple and sensitive methods for the determination of isoxicam is of great importance for toxicological and pharmaceutical purposes.

A few numbers of analytical techniques have been available for the estimation of isoxicam in pharmaceutical formulations and biological fluids, including spectrophotometry [5], thin layer chromatography (TLC) [6], high-performance thin layer chromatography (HPTLC) [7], capillary electrophoresis (CE) [7], high-performance liquid chromatography (HPLC) [8–11] and liquid chromatography-tandem mass spectrometry (HPLC-MS) [12]. Pharmacopoeias do not provide any monograph for isoxicam [13]. However, all these assay methodologies have some drawbacks. Spectrophotometric method reported in the literature suffers from disadvantages like extraction and pre-concentration procedure. The chromatography technique possesses high selectivity and sensitivity, but all of them involve expensive instrumental set up and toxic solvents; moreover, time-consuming extraction and separation procedures are also needed, which make these techniques not suitable for routine analysis. CL combined with the flow-injection method has received much attention for the analysis of organic and inorganic species in a variety of fields owing to its high sensitivity, wide linear range and relatively simple and inexpensive instrumentation [14–19]. To the best of our knowledge, however, there is no work in the literature reported about the CL method for the analysis of isoxicam in either biological fluids or pharmaceutical formulations. The object of the present work, therefore, has been to investigate the use of CL in the detection of isoxicam in pharmaceutical preparations and biological fluids.

Some transition metals in their highest oxidation states such as trivalent silver has been reported, generally can be stabilized by chelating with suitable polydentate ligands for their unstable character in an aqueous solution. Diperiodatoargentate(III) is powerful oxidant in a medium with an appropriate pH value. The polydentate chelates of trivalent silver takes on character of strong oxidation with a redox potential of 1.74 V [20] in alkaline medium, because of their strong versatile nature of the two electron oxidants [20,21]. Although there are many reports

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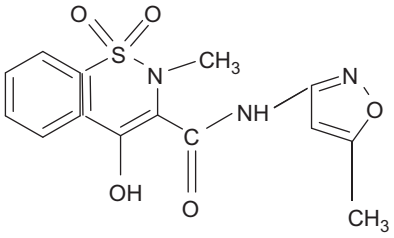

Fig. 1. The structure of isoxicam.

concerning the use of diperiodatoargentate(III) as oxidant in alkaline medium, the use of diperiodatoargentate(III) in CL analysis is relatively few. It was found that strong CL can be generated after isoxicam is mixed with diperiodatoargentate(III) in alkaline medium while fluorescein and CTAB are present. Based on these observations, a novel enhanced FI-CL assay for the rapid determination of trace amounts of isoxicam has been developed for the first time. It is noteworthy the result of interference studies shows that the developed method offers a good accuracy and precision and has been satisfactorily applied to the determination of isoxicam in the commercial preparations and biological fluids. The possible CL emission mechanism is also discussed briefly.

2. Experimental

2.1. Reagents

All the reagents were of analytical reagent grade and were used without further purification. All solutions were prepared with doubly distilled water. Isoxicam and cetyltrimethylammonium bromide (CTAB) were purchased from Sigma-Aldrich (Germany). Potassium peroxydisulfate was obtained from Tianjin Guangfu Fine Chemical Research Institute (Tianjin, China). Silver nitrate and potassium hydroxide were purchased from Tianjin Damao Chemical Reagent Company (Tianjin, China). Sodium periodate and sodium nitrate were the products of Shanghai Yuanji Chemical Co. Ltd. (Shanghai, China). Fluorescein was from Shanghai Chemical Reagent Co. Ltd., China (Shanghai, China).

Diperiodatoargentate(III) was synthetized using the method suggested by Balikungeri et al. [22]. In briefly, silver nitrate (1.36 g), sodium periodate (3.42 g), potassium peroxydisulfate (3.0 g) and potassium hydroxide (8.0 g) were taken in a 250 ml round bottomed flask. 100 ml of water were added to this mixture. The mixture was heated to boiling while stirring. After 15 min of boiling an orangish-yellow froth was obtained and the mixture was heated for another 15 min. The mixture was left to cool to room temperature and filtered through a Gooch crucible (the complex is instantaneously reduced on a filter paper). The solution was cooled in an ice 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 attain room temperature. In order to isolate the complex, 40 ml of sodium nitrate solution (50%, in excess) were added to the solution and the mixture left to crystallize. Almost immediately crystals started appearing and crystallization is complete when the supernatant liquid is colorless. The crystals were filtered and washed several times with water until the complex itself starts dissolving, which is indicated by the orange–red drops being formed under the crucible. In this way one can be sure of eliminating sodium and potassium hydroxide since this complex is insoluble in concentrated hydroxide solutions. The diperiodatoargentate(III) solutions were freshly prepared by dissolving amount of the complex in 0.01 mol/l potassium hydroxide solution before experiment. The diperiodatoargentate(III) was characterized from its UV–visible spectrum, exhibited two peaks at 253 and 362 nm. These spectral features were identical to those reported earlier for diperiodatoargentate(III) [22]. The concentration of the diperiodatoargentate(III) solution was determined by the absorbency at 363 nm (molar absorptivity $\varepsilon = 1.26 \times 10^4$ l/mol cm) [23].

The 0.1 mg/ml standard solution of isoxicam was prepared by dissolving appropriate amount of isoxicam in 3.0×10^{-3} mol/l potassium hydroxide solution and kept at about 4 °C in a dark bottle. Working standard solutions were prepared by appropriately diluting the stock solution with water before use. The 3 mmol/l fluorescein stock solution was prepared daily by dissolving 0.0996 g fluorescein in 0.01 mol/l potassium hydroxide solution and diluting to 100 ml in a brown measuring flask with the same concentration potassium hydroxide solution. The 0.1 mol/l CTAB stock solution was freshly prepared by dissolving CTAB in water.

2.2. Apparatus

The schematic diagram of the FI-CL system used in this work is shown in Fig. 2. A peristaltic pump was used to deliver all the chemicals at a flow rate of 3.5 ml min^{-1}. Polytetrafluoroethylene (PTFE) tubing (0.8 mm i.d.) was employed to connect all the components of the flow system. Injection was accomplished by means of a six-way valve equipped up with a 100 μl sample loop. The flow cell was a coil of glass tubing located directly facing the detection window of the photomultiplier tube. The CL signal was detected with an IFFM-D multifunction chemiluminescence analyzer (Xi'an Remex Analysis Instrument Co. Ltd, Xi′an, China). The absorption spectra were detected with an UV-2401 spectrophotometer (Shimadzu, Japan). The CL spectrum was recorded with an F-4500 fluorescence spectrofluorometer (Hitachi, Japan).

2.3. Procedures

In order to obtain good stability, the instruments were run for at least 15 min before the first measurement was made. As shown in Fig. 2, the mixture of isoxicam and fluorescein solution was injected into the carrier stream (CTAB solution) by a six-way valve quantitatively, which was then merged with the stream of diperiodatoargentate(III) solution. The mixed solution was delivered to the flow cell, producing CL emission. The CL signal produced in the flow cell was recorded by CL analyzer. The concentration of isoxicam was

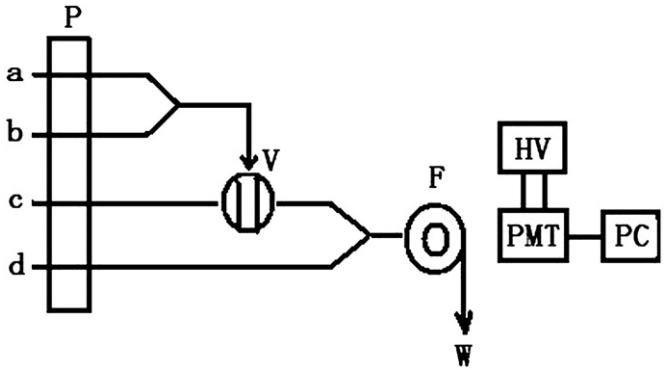

Fig. 2. Schematic diagram of flow injection CL analysis system. *P*, peristaltic pump; *V*, sample injection valve; *F*, flow cell; HV, high voltage; PMT, photomultiplier tube; *W*, waste; PC, personal computer; a, isoxicam solution; b, fluorescein solution; c, CTAB solution; d, diperiodatoargentate(III) + KOH solution.