Flow injection chemiluminescence determination of loxoprofen and naproxen with the acidic permanganate-sulfite system

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Abstract: A novel flow injection chemiluminescence (CL) method for the determination of loxoprofen and naproxen was proposed based on the CL system of KMnO4 and Na2SO3 in acid media. The CL intensity of KMnO4-Na2SO3 was greatly enhanced in the presence of loxoprofen and naproxen. Under optimized conditions, the CL intensity was linear with loxoprofen and naproxen concentration in the range of 7.0×10^{-8} - 1.0×10^{-5} g/mL and 2.0×10^{-7} - 4.0×10^{-4} g/mL with the detection limit of 2.0×10^{-8} g/mL and 3.0×10^{-8} g/mL (S/N = 3), respectively. The relative standard deviations were 2.39% and 1.37% for 5.0×10^{-7} g/mL naproxen and 5.0×10^{-7} g/mL loxoprofen (n = 10), respectively. The proposed method was satisfactorily applied to the determination of loxoprofen and naproxen in pharmaceutical preparations.

Keywords: chemiluminescence; KMnO4; loxoprofen; naproxen

1 Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of analgesics and anti-inflammatory drugs that are most commonly used around the world for treating inflammatory diseases and musculoskeletal injuries for their analgesic and antipyretic effects. Recently, NSAIDs have gained more attention because they can reduce the risk of developing Alzheimer’s disease and various tumors [1-5]. NSAIDs are a large family of compounds according to their chemical structures. Regardless of their structural differences, NSAIDs induce mostly of the same therapeutic functions as well as side effects [6].

Laxoprofen and naproxen are well-established NSAIDs which belong to the arylpropionic acid family, the structures as described in Figure 1. The two arylpropionic acid derivatives have been used widely in clinic and other fields. Up to now, many researchers interested in their possible side effects considerably. At the same time, these compounds are environmental pollutants due to their residue levels in water [7,8]. Therefore, it is very important to develop highly sensitive analytical methods for the analysis of loxoprofen and naproxen. Many methods have been developed for the assay of loxoprofen and naproxen, including spectrometry [9,10], HPLC [11-13], HPLC-MS [14-16], CE [17,18], and GC-MS [19,20]. Some of methods, however, have shown considerable shortcomings, such as bulky instrumentation, large sample, and time consumption.

Chemiluminescence (CL) is a simple and rapid method which does not require sophisticated instruments and too many chemical reagents. CL method has been developed to detect arylpropionic acid derivatives, such as ketoprofen, naproxen, ibuprofen, and fenbufen [21-25]. To the best of our knowledge, CL method for the detection of loxoprofen has not been reported.

In this paper, a novel flow injection chemiluminescence method for the determination of loxoprofen and naproxen is proposed based on the CL reaction of KMnO4 and Na2SO3 in acid media. The CL intensity of KMnO4-Na2SO3 was greatly enhanced in the presence of loxoprofen and naproxen. The mechanism of the CL reaction was studied and the conditions were optimized. The proposed method was applied to the determination of loxoprofen and naproxen in pharmaceutical preparations.

2 Materials and methods

2.1 Reagents

The stock solutions (1.0×10^{-3} g/mL) of loxoprofen and naproxen (National Institute for the Control of Pharmaceutical and Biological Products, Beijing, China) were prepared by dissolving 0.1000 g of each compound in double distilled water and diluting to 100 mL. The stock solutions were stored in a refrigerator and kept from light. The testing solutions were prepared by appropriate dilution of these stock solutions with water before use.

KMnO4 stock solution (0.01 M) was prepared by dissolving 0.1580 g of KMnO4 (Xi’an Chemical Reagent Factory, Xi’an, China) in a 0.1 M sulfuric acid solution and diluting to 100 mL with water. A Na2SO3 stock solution (5×10^{-3} M) was prepared by dissolving 0.0630 g of sodium sulfite...
(Xi'an Chemical Reagent Factory, Xi'an, China) in water and diluting to 100 mL with water. The working solutions were obtained by a series of dilutions of the stock solution with water.

All chemicals used were of analytical grade. Double distilled water was used during the entire experiment procedure. Naproxen tablets (250 mg/tablet) were provided by Shaanxi LanHuaQiFoShan Pharmaceutical Co., Ltd. (Shaanxi, China). Loxoprofen sodium capsules (60 mg/capsule) were provided by Shandong Qidu Pharmaceutical Co., Ltd. (Shandong, China).

Ten capsules (tablets) of loxoprofen and naproxen were accurately weighed, and then ground to fine powder, respectively. A tablet sample equivalent to approximately 250 mg naproxen and 60 mg loxoprofen was weighed accurately, and then dissolved in water. Each solution was filtered and the corresponding residue was washed several times with water. All the solutions were collected. When the level of loxoprofen and naproxen was above the calibration ranges, samples were appropriately diluted with water prior to the assay.

2.2 Apparatus

Figure 2 is the schematic diagram of the flow injection CL (FI-CL) system. A peristaltic pump was used for delivering the sample solution and Na$_2$SO$_4$ solution. Another peristaltic pump was applied to deliver KMnO$_4$ solution. All components were connected with PTFE tubing (0.8 mm i.d.) in the flow system. Reagent solutions were injected into the flow system by a six-way injection valve. A photomultiplier tube was employed to detect the CL intensity. The CL signal was recorded and treated using IFFM-E type data processing system (Xi'an Remax Electronic Science-tech Co., Ltd., China).

The UV spectrum was obtained using an UV-vis spectrophotometer (Shanghai Spectrum Instruments Co., Ltd., China).

2.3 Procedures

As shown in Figure 2, flow lines were inserted into the sample/standard solution, loxoprofen or naproxen solution, Na$_2$SO$_4$ solution and KMnO$_4$ solution, respectively. The pump was started to wash the whole flow system until a stable baseline was recorded. Then a sample/standard solution was injected into the Na$_2$SO$_4$ solution stream. The stream was merged with KMnO$_4$ solution in the flow cell to produce CL emission. The signal was recorded using a compatible computer connected to the PMT. The concentration of sample was quantified by the increase of CL intensity, calculated as $\Delta I = I - I_0$, where $I$ is the net CL signal of the system in the presence of sample and $I_0$ is the CL intensity of the system in the absence of sample.

3 Results and discussion

3.1 CL intensity-time profile

The CL kinetic characteristics of the KMnO$_4$-Na$_2$SO$_4$-sample system were investigated. The results are shown in Figure 3 and Figure 4. The results showed that a strong enhancement of the CL emission of the KMnO$_4$-Na$_2$SO$_4$ reaction was observed in the presence of naproxen and loxoprofen respectively. Therefore, the addition of two kinds of arylopropionic acid derivatives could facilitate the KMnO$_4$-Na$_2$SO$_4$ CL reaction and greatly enhance light emission.

Figure 3 Kinetic CL intensity-time profile of KMnO$_4$-Na$_2$SO$_4$-naproxen reaction.
### 3.2 Optimization of experimental conditions

#### 3.2.1 Effect of instrumental parameters

The instrumental parameters, including the flow rate, the ratio of peristaltic pump1 to peristaltic pump2 (V₁/V₂), and the length (Lₜ) from three ways “T” to the flow cell, were optimized. The length (Lₜ) of 6 cm and the flow rate of 1.6 mL/min could give a steady baseline and the maximum CL intensity, which were chosen for further study.

Sulfuric acid was added to the KMnO₄ solution to test the effect on the CL signal. The maximum and most stable CL signal was obtained when sulfuric acid was added. Hence, H₂SO₄ was chosen for further work. And then, the effect of H₂SO₄ concentration on the CL intensity was studied over the range of 0.01 M to 0.2 M. The results showed that the maximum CL intensity was obtained with 0.1 M H₂SO₄ (Figure 6). So, 0.1 M H₂SO₄ was selected as the suitable medium for subsequent work.

The effect of V₁/V₂ on the CL signal was investigated in the range of 0.5 to 2, and the results showed that the maximum CL emission intensity was obtained when the ratio was up to 1.0 (as shown in Figure 5). Therefore, the ratio of 1.0 was selected for subsequent procedures.

In this CL system, potassium permanganate in sulfuric acid which is used as the oxidant can offer both the maximum CL signal and the best signal-to-background ratio. Therefore, the effect of KMnO₄ concentration in 0.1 M sulfuric acid medium on the relative CL intensity was studied in the range of 1.0×10⁻⁶ M to 1.0×10⁻² M. The results are shown in Figure 7. The results showed that 1.0×10⁻⁴ M could give rise to the larger CL response and lower background signal. So, the optimum concentration of KMnO₄ was chosen as 1.0×10⁻⁴ M.

#### 3.2.2 Effect of chemical variables

The chemical variables, including the concentrations of potassium permanganate and sodium sulfite, and the different inorganic acid media, were investigated.

It was observed that the CL signal of KMnO₄-Na₂SO₃ system was stronger in acid solution than in neutral or basic solutions. Five different acids (i.e. HCl, HNO₃, H₃PO₄, HAc, and H₂SO₄) with different concentrations were added to the KMnO₄ solution to test the effect on the CL signal. The maximum and most stable CL signal was obtained when sulfuric acid was added. Hence, H₂SO₄ was chosen for further work. And then, the effect of H₂SO₄ concentration on the CL intensity was studied over the range of 0.01 M to 0.2 M. The results showed that the maximum CL intensity was obtained with 0.1 M H₂SO₄ (Figure 6). So, 0.1 M H₂SO₄ was selected as the suitable medium for subsequent work.

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The effect of Na₂SO₃ concentration on the CL intensity was investigated in the range of 1.0×10⁻⁴ M to 1.0×10⁻² M. The results are shown in Figure 8. The results showed that the chemiluminescence intensity increased with the increase of Na₂SO₃ concentration when it was lower than 5.0×10⁻³ M, with a higher signal-to-noise ratio. Thus, 5.0×10⁻³ M was chosen for further study.
3.3 Analytical characteristics

3.3.1 Linearity

Under the optimized conditions, the calibration curves for the determination of naproxen and loxoprofen were established by triplicate injections of different concentration samples. The linear dynamic range, regression equation, correlation coefficient, and limit of detection (LOD) of each compound are listed in Table 1.

| NSAIDs   | Linear range (g/mL) | Regression equation (unit of C is µg/mL) | Correlation coefficient | LOD (g/mL) |
|----------|---------------------|-----------------------------------------|-------------------------|------------|
| Naproxen | \(7.0 \times 10^{-8} - 1.0 \times 10^{-4}\) | \(\Delta I = 188.58C + 44.6\) | 0.9979 | \(2.0 \times 10^{-8}\) |
| Loxoprofen | \(2.0 \times 10^{-7} - 4.0 \times 10^{-6}\) | \(\Delta I = 58.86C + 13.0\) | 0.9958 | \(3.0 \times 10^{-8}\) |

Figure 8 Effect of \(\text{Na}_2\text{SO}_4\) concentration on the relative CL intensity. \(1.0 \times 10^{-4}\) M naproxen + \(1.0 \times 10^{-4}\) M \(\text{KMnO}_4\) in 0.1 M \(\text{H}_2\text{SO}_4\) medium.

3.3.2 Precision

The precision of the proposed method was obtained by analyzing samples containing \(5.0 \times 10^{-7}\) g/mL naproxen and \(5.0 \times 10^{-7}\) g/mL loxoprofen respectively. On three consecutive days, each sample was injected ten times. The results are listed in Table 2.

| NSAIDs   | Concentration found (\(\times 10^{-7}\) g/mL) | RSD (%) |
|----------|---------------------------------------------|---------|
| Naproxen | 0.8 \(0.81 \pm 0.02\) | 2.05    |
|          | 5.0 \(5.07 \pm 0.12\) | 2.39    |
|          | 50 \(52.25 \pm 2.37\) | 4.55    |
|          | 1.0 \(1.00 \pm 0.03\) | 3.19    |
| Loxoprofen | 5.0 \(5.05 \pm 0.07\) | 1.37    |
|          | 10 \(10.10 \pm 0.14\) | 1.43    |

3.3.3 Interference

In order to assess the analytical applicability possibility of the CL method described above, the interference of different metal ions and some excipients used in pharmaceutical preparations on the CL intensity was investigated by analyzing the solutions of \(1.0 \mu g/mL\) naproxen and \(1.0 \mu g/mL\) loxoprofen, respectively. The tolerable limit of a foreign species was taken as a relative error less than 5%. The results showed that no interference could be observed when the sample included up to a 1000-fold \(\text{Mg}^{2+}\), \(\text{Ca}^{2+}\), \(\text{Na}^{+}\), \(\text{NO}_3^{-}\), 100-fold \(\text{Al}^{3+}\), starch, glucose, 10-fold \(\text{CO}_3^{2-}\), sucrose, and uric acid.

3.4 Analytical application

The proposed method was applied to the determination of naproxen and loxoprofen in commercial pharmaceutical formulations. The samples were determined by standard addition method. As shown in Table 3, the obtained recoveries were in the range of 98.5% to 104.0%. As shown in Table 4, the results showed that there were no significant differences between the nominal content values and those obtained by the proposed method.

| NSAIDs pharmaceutical preparation | Nominal content (g/tablet) | Proposed FL-CL method (g/tablet) |
|-----------------------------------|-----------------------------|----------------------------------|
| Naproxen tablets                  | 0.25                        | 0.23 ± 0.015                     |
| Loxoprofen tablets                | 0.060                       | 0.058 ± 0.0014                   |

Note: Values are the averages of three measurements ± SD (amount of NSAIDs tablets [g/tablet]).

3.5 Possible mechanism

Grinberg first used the potassium permanganate as the chemiluminescence reagent in analytical chemistry in 1920. And then, there are some discussions about the mechanism of this kind of reaction and the corresponding emitting species in the literature. The emitting species of the potassium permanganate CL reaction can be broadly grouped as follows: manganese species, singlet oxygen, analyte oxidation products, and compounds that receive energy from an excited intermediate of the reaction [26]. Excited sulphur dioxide molecules are often considered as the CL emitters when sodium sulfite reacts with potassium permanganate [27]. Meixner and Jaeschke [28] proposed an alternative
mechanism, which can be explained as follows:

\[
\begin{align*}
\text{HSO}_3^- + \text{MnO}_4^- &\rightarrow \text{HSO}_4^- + \text{MnO}_4^{2-} \\
2\text{HSO}_3^- &\rightarrow \text{S}_2\text{O}_5^{2-} + 2\text{H}^+ \\
\text{S}_2\text{O}_5^{2-} &\rightarrow \text{SO}_4^{2-} + \text{SO}_2^+ \\
\text{SO}_2^+ &\rightarrow \text{SO}_2 + h\nu
\end{align*}
\]

It is supposed that sulfite acts as a reductant to produce an excited molecule of sulfur dioxide, which emits radiation in the range of 450 – 600 nm [29]. The emission intensity could be sensitized with fluorescent compounds and non-fluorescence compounds [30,31].

In this work, it was found that naproxen and loxoprofen could increase the CL intensity of potassium permanganate and sulfite. In order to illustrate the possible mechanism of the CL reaction, UV-vis absorption spectra of different systems were studied. As shown in Figure 9, the results showed that naproxen could react with KMnO₄ while it could not react with Na₂SO₃. Figure 10 shows that loxoprofen could also react with KMnO₄ while it could not react with Na₂SO₃. So, we deduced that the two CL reaction mechanisms are the same because the two arylpropionic acid derivatives can react with KMnO₄. On the basis of the previously reported results and the results obtained in this study, we deduced the possible CL mechanism of this system, which was shown as follows.

\[
\begin{align*}
\text{MnO}_4^- + \text{H}^+ + \text{SO}_3^{2-} &\rightarrow \text{SO}_4^{2-} + \text{Mn(II- IV)} + \text{H}_2\text{O} \\
\text{SO}_4^{2-} &\rightarrow \text{SO}_2^+ + h\nu (532 \text{ nm}) \\
\text{Loxoprofen (naproxen) + MnO}_4^- &\rightarrow [\text{Loxoprofen}]_{\text{ox}} (\text{[naproxen]}_{\text{ox}}) \\
[\text{Loxoprofen}]_{\text{ox}} (\text{[naproxen]}_{\text{ox}}) + \text{HSO}_3^- &\rightarrow \text{HSO}_4^- + \text{Loxoprofen(naproxen)} \\
2\text{HSO}_3^- &\rightarrow \text{S}_2\text{O}_5^{2-} + 2\text{H}^+ \\
\text{S}_2\text{O}_5^{2-} &\rightarrow \text{SO}_4^{2-} + \text{SO}_2^+ \\
\text{SO}_2^+ &\rightarrow \text{SO}_2 + h\nu (532 \text{ nm})
\end{align*}
\]

Figure 9 Absorption spectra of the KMnO₄-Na₂SO₃-naproxen system.

4 Conclusions

In this paper, a novel CL method for the determination of loxoprofen and naproxen has been developed based on the CL reaction of KMnO₄ and Na₂SO₃ in acid media. Compared to other methods for the determination of loxoprofen and naproxen, this method offers potential advantages of good linearity, higher sensitivity, and good precision. The proposed method has been satisfactorily applied to the determination of loxoprofen and naproxen in pharmaceutical preparations. Moreover, the possible mechanism of this CL system is proposed.

Figure 10 Absorption spectra of the KMnO₄-Na₂SO₃-loxoprofen.

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