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ORIGINAL ARTICLES

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

Li-Juan Wang[1,2], Yu-Hai Tang[2*], Yang-Hao Liu[2]

[1] *Medical School, Xi'an Jiaotong University, Xi'an 710061, China;*
[2] *Institute of Analytical Sciences, Xi'an Jiaotong University, Xi'an 710061, China.*

Abstract: A novel flow injection chemiluminescence (CL) method for the determination of loxoprofen and naproxen was proposed based on the CL system of $KMnO_4$ and Na_2SO_3 in acid media. The CL intensity of $KMnO_4$-Na_2SO_3 was greatly enhanced in the presence of loxoprofen and naproxen. The mechanism of the CL reaction was studied by the kinetic process and UV-vis absorption and the conditions were optimized. Under optimized conditions, the CL intensity was linear with loxoprofen and naproxen concentration in the range of $7.0\times10^{-8}-1.0\times10^{-5}$ g/mL and $2.0\times10^{-7}-4.0\times10^{-6}$ 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; $KMnO_4$; 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].

Loxoprofen 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 $KMnO_4$ and Na_2SO_3 in acid media. The CL intensity of $KMnO_4$-Na_2SO_3 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.

$KMnO_4$ stock solution (0.01 M) was prepared by dissolving 0.1580 g of $KMnO_4$ (Xi'an Chemical Reagent Factory, Xi'an, China) in a 0.1 M sulfuric acid solution and diluting to 100 mL with water. A Na_2SO_3 stock solution (5×10^{-3} M) was prepared by dissolving 0.0630 g of sodium sulfite

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* Corresponding author. E-mail: tyh57@mail.xjtu.edu.cn

(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 obove the calibration ranges, samples were appropriately diluted with water prior to the assay.

Figure 1 Structures of loxoprofen and naproxen

4-(6-methoxy-2-naphthy 1)-2-butanone
Lexoprofen

(+)-2-(6-methoxy-2-naphthy 1) propionic acid
Naproxen

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_2SO_3 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).

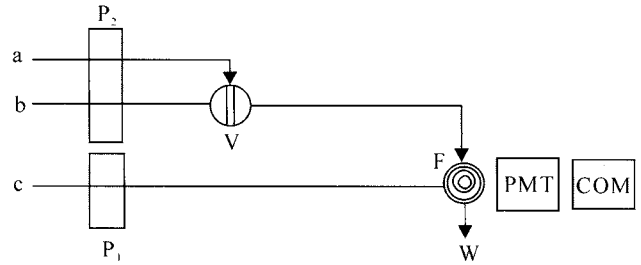

Figure 2 Schematic diagram of the FI-CL system for the determination of naproxen and loxoprofen. a, sample solution; b, Na_2SO_3 solution; c, $KMnO_4$ solution; P_1 and P_2, peristaltic pump; V, six-way valve; F, flow cell; PMT, photomultiplier tube; COM, computer; W, waste solution.

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_2SO_3 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_2SO_3 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_2SO_3-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_2SO_3 reaction was observed in the presence of naproxen and loxoprofen respectively. Therefore, the addition of two kinds of arylpropionic acid derivatives could facilitate the $KMnO_4$-Na_2SO_3 CL reaction and greatly enhance light emission.

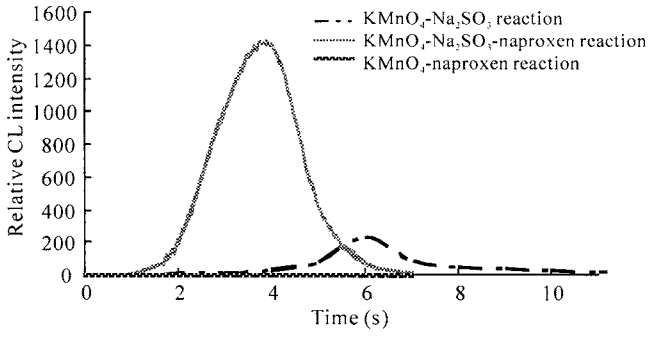

Figure 3 Kinetic CL intensity-time profile of $KMnO_4$-Na_2SO_3-naproxen reaction.

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 (V_1/V_2), and the length (L_0) from three ways "T" to the flow cell, were optimized. The length (L_0) 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.

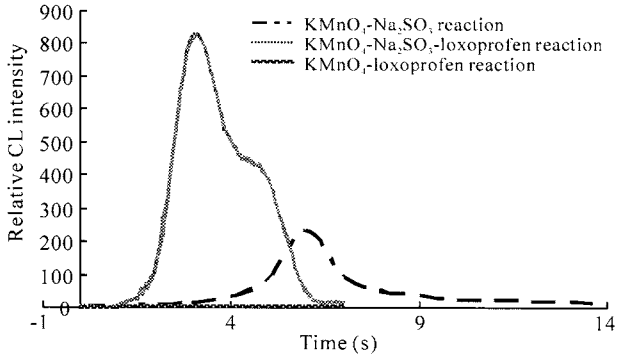

Figure 4 Kinetic CL intensity-time profile of $KMnO_4$-Na_2SO_3-loxoprofen reaction.

The effect of V_1/V_2 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.

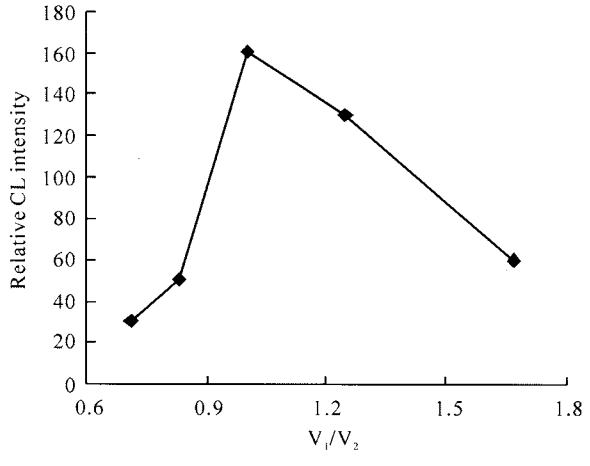

Figure 5 Effect of V_1/V_2 ratio on the relative CL intensity. 1.0×10^{-4} M $KMnO_4$ (0.1 M H_2SO_4) + 1.0×10^{-6} M naproxen + 5.0×10^{-3} M Na_2SO_3.

3.2.2 Effect of chemical variables

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

It was observed that the CL signal of $KMnO_4$-Na_2SO_3 system was stronger in acid solution than in neutral or basic solutions. Five different acids (i.e. HCl, HNO_3, H_3PO_4, HAc, and H_2SO_4) with different concentrations were added to the $KMnO_4$ solution to test the effect on the CL signal. The maximum and most stable CL signal was obtained when sulfuric acid was added. Hence, H_2SO_4 was chosen for further work. And then, the effect of H_2SO_4 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 H_2SO_4 (Figure 6). So, 0.1 M H_2SO_4 was selected as the suitable medium for subsequent work.

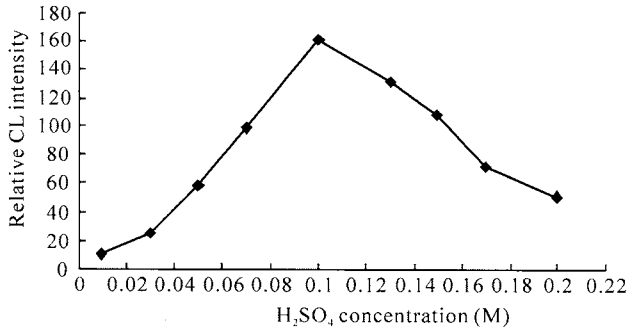

Figure 6 Effect of H_2SO_4 concentration on the relative CL intensity. 1.0×10^{-4} M $KMnO_4$ + 1.0×10^{-6} M naproxen + 5.0×10^{-3} M Na_2SO_3.

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 the background ratio. Therefore, the effect of $KMnO_4$ 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 $KMnO_4$ was chosen as 1.0×10^{-4} M.

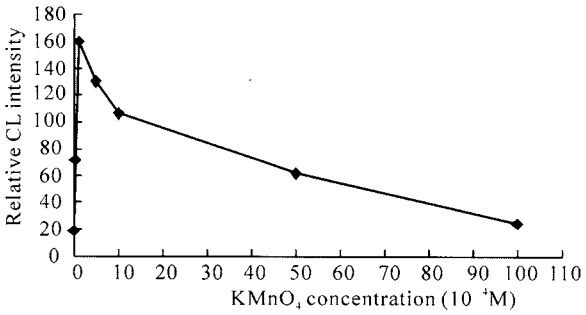

Figure 7 Effect of $KMnO_4$ concentration on the relative CL intensity. 1.0×10^{-6} M naproxen + 5.0×10^{-3} M Na_2SO_3.

The effect of Na_2SO_3 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 Na_2SO_3 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.

Table 1 The linear dynamic range, regression equation, correlation coefficient, and LOD of naproxen and loxoprofen

NSAIDs	Linear range (g/mL)	Regression equation (unit of C is μg/mL)	Correlation coefficient	LOD (g/mL)
Naproxen	$7.0\times10^{-8}-1.0\times10^{-5}$	$\Delta I = 168.58C + 44.6$	0.9979	2.0×10^{-8}
Loxoprofen	$2.0\times10^{-7}-4.0\times10^{-6}$	$\Delta I = 58.6C + 13.0$	0.9958	3.0×10^{-8}

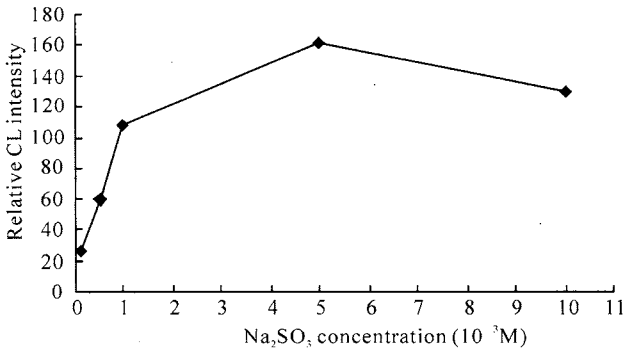

Figure 8 Effect of Na_2SO_3 concentration on the relative CL intensity. 1.0×10^{-6} M naproxen + 1.0×10^{-4} M $KMnO_4$ in 0.1 M H_2SO_4 medium.

3.3.2 Precision

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

Table 2 The precision in the determination of naproxen and loxoprofen standard substance

NSAIDs	Concentration ($\times10^{-7}$ g/mL)	Concentration found ($\times10^{-7}$ g/mL)	RSD (%)
Naproxen	0.8	0.81 ± 0.02	2.05
	5.0	5.07 ± 0.12	2.39
	50	52.25 ± 2.37	4.55
Loxoprofen	1.0	1.00 ± 0.03	3.19
	5.0	5.05 ± 0.07	1.37
	10	10.10 ± 0.14	1.43

3.3.3 Interference

In order to assess the analytical application 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 μg/mL naproxen and 1.0 μg/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 Mg^{2+}, Ca^{2+}, Na^+, NO_3^-, 100-fold Al^{3+}, starch, glucose, 10-fold 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.

Table 3 Recovery rate of externally added (1×10^{-6} g/mL) naproxen and loxoprofen in pharmaceutical preparations

NSAIDs	Original concentration ($\times10^{-6}$ g/mL)	Added concentration ($\times10^{-6}$ g/mL)	Found concentration ($\times10^{-6}$ g/mL)	Recovery rate (%)	Average of recovery rate (%)
Naproxen	1.0	0	0.97		101.8
		1.0	1.99	102.0	
		2.0	3.03	103.0	
		3.0	3.98	100.3	
Loxoprofen	1.0	0	0.95		100.6
		1.0	1.99	104.0	
		2.0	2.92	98.5	
		3.0	3.93	99.3	

Table 4 Analysis results of the two NSAIDs in pharmaceutical preparations

NSAIDs pharmaceutical preperation	Nominal content (g/tablet)	Proposed FI-CL method (g/tablet)
Naprofen 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:

$$HSO_3^- + MnO_4^- \longrightarrow \cdot HSO_3 + MnO_4^{2-}$$
$$2HSO_3 \cdot \longrightarrow S_2O_6^{2-} + 2H^+$$
$$S_2O_6^{2-} \longrightarrow SO_4^{2-} + SO_2^*$$
$$SO_2^* \longrightarrow SO_2 + h\nu$$

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 $KMnO_4$ while it could not react with Na_2SO_3. Figure 10 shows that loxoprofen could also react with $KMnO_4$ while it could not react with Na_2SO_3. So, we deduced that the two CL reaction mechanisms are the same because the two arylpropionic acid derivatives can react with $KMnO_4$. 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.

$$MnO_4^- + H^+ + SO_3^{2-} \longrightarrow SO_2^* + Mn(\text{II}-\text{IV}) + H_2O$$
$$SO_2^* \longrightarrow SO_2 + h\nu\ (532\ nm)$$
$$\text{Loxoprofen (naproxen)} + MnO_4^- \longrightarrow [\text{Loxoprofen}]_{ox}\ ([\text{naproxen}]_{ox})$$
$$[\text{Loxoprofen}]_{ox}([\text{naproxen}]_{ox}) + HSO_3^- \longrightarrow HSO_3 \cdot + \text{Loxoprofen(naproxen)}$$
$$2HSO_3 \cdot \longrightarrow S_2O_6^{2-} + 2H^+$$
$$S_2O_6^{2-} \longrightarrow SO_4^{2-} + SO_2^*$$
$$SO_2^* \longrightarrow SO_2 + h\nu\ (532\ nm)$$

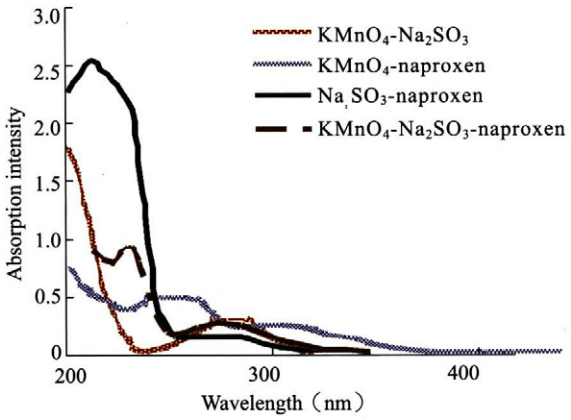

Figure 9 Absorption spectra of the $KMnO_4$-Na_2SO_3-naproxen system.

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 $KMnO_4$ and Na_2SO_3 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.

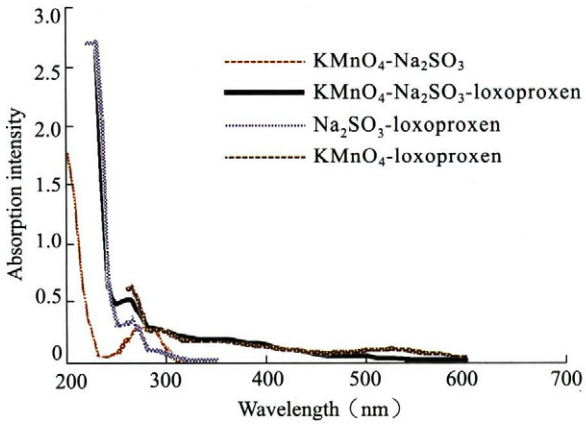

Figure 10 Absorption spectra of the $KMnO_4$-Na_2SO_3-loxoproxen.

Acknowledgments

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