Direct Chemiluminescence Determination of Oxymorphone Using Potassium Permanganate and Polyphosphoric Acid

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A simple and sensitive chemiluminescence (CL) method was developed for direct quantification of oxymorphone, a μ opioid agonist that is approximately 10 times more potent than morphine. In this method, potassium permanganate in polyphosphoric acid was used as CL reagent. Using this method, oxymorphone can be determined over the concentration ranges of 13.5-337.8 ng ml^{-1} and 0.34-6.76 μg ml^{-1} with a sampling rate of 45 samples h^{-1}. The limit of detection was 3.5 ng ml^{-1} (signal to noise =3) and the percentage of relative standard deviations (in 9 replicate measurements) were 3.1% for 135.1 ng ml^{-1} and 3.6% for 1.4 μg ml^{-1} oxymorphone. The method is applied to human plasma and synthetic samples. The CL mechanism has been proposed using UV-Vis, fluorescence and CL spectra. In this study, detectability of oxymorphone in some other CL systems such as Ce(IV)-H$_2$SO$_4$, luminol-H$_2$O$_2$, Ru(phen)$_3^{2+}$-Ce(IV) and permanganate-SO$_3^{2-}$ is investigated. CL intensities of twelve narcotics or related drugs were also investigated in the proposed CL system.

INTRODUCTION

Narcotic analgesics, as pain relieving drugs, can cause numbness and induce a state of unconsciousness. They bind to the opioid receptors present in the central and peripheral nervous system [1]. Oxymorphone (Fig. 1), a semisynthetic μ-opioid agonist, is considered a more potent opioid than its parent compound, morphine [2]. It is indicated for the relief of moderate to severe pain and also as a preoperative medication to alleviate apprehension, maintain anaesthesia and as an obstetric analgesic [3]. It is also recommended for acute pain control in dogs [4]. Oxymorphone overdose can be fatal especially for children and adults using the medicine without a prescription [5]. Peak plasma concentrations for administered volunteers with 1.5 mg oxymorphon is reported 164 ng ml^{-1} and 91 ng ml^{-1} after 24 h and 36 h, respectively, and for 3.0 mg dose it is reported 435 and 120 ng ml^{-1} after 24 h and 36 h, respectively [6]. The
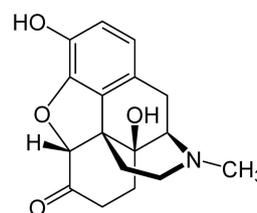

Fig. 1. Chemical structure of oxymorphone.

estimated minimum lethal dose of oxymorphone is reported 50 mg [6].

Different chromatographic methods, such as high-performance liquid chromatography (HPLC) [7,8], liquid chromatography tandem mass spectrometry (LC-MS/MS) [9-17], LC-MS [18] and GC-MS [19,20] have been proposed for the determination of oxymorphone in its mixture with related compounds. To the best of our knowledge, non-chromatographic methods have not been reported in the literature for the determination of oxymorphone up to now.

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Chemiluminescence (CL), emission of light from a chemical reaction, offers a simple, low cost and sensitive means to quantify a wide variety of compounds [21]. Over the past decades, many CL systems have been explored, however, only a limited number of them have been widely used for analytical applications such as peroxyoxalate [22,23], luminol [24,25], Ru(II) complexes [26,27] and potassium permanganate [28,29]. Some narcotic compounds such as naloxone [30], noscapine [31], morphine [32,33], heroine [34], oripavine and pseudomorphine [35,36], heroine [36] and papaverine [37], are determined using CL system of acidic potassium permanganate with aid of a fluorophore, a fluorescent chemical compound that can re-emit light upon light excitation. Using this reagent and without a fluorophore, only limited number of narcotic analgestics have been determined up to now, such as morphine [38], naloxone [39], naltrexone [40], pseudomorphine [36], buprenorphine [41], heroine [42] and codeine [43].

We describe here a simple and rapid CL method for the quantification of oxymorphone that does not require complex instrument. The method is based on direct oxidation of oxymorphone by potassium permanganate in polyphosphoric acid solution. This method was applied for the determination of oxymorphone in synthetic injections and human plasma. To the best of our knowledge, this report describes the first application of a spectroscopic method for the determination of oxymorphone.

EXPERIMENTAL

Materials and Methods

All solutions and dilutions were prepared using deionized water. Oxymorphone and other related compounds were purchased from Temad Co. (Iran). The stock solution of oxymorphone was prepared by dissolving oxymorphone hydrochloride into deionized water in a 100.0 ml volumetric flask to give a 338.0 μg ml^{-1} solution of oxymorphone. Permanganate solution (0.006 M) was daily prepared by dissolving 0.0920 g of KMnO$_4$ (Chem lab, Belgium) in calculated volume of 2.0 M polyphosphoric acid (Merck, Germany) solution and was diluted with water in a 100-ml volumetric flask.

Methanol was purchased from Chem Lab., Belgium. The plasma samples obtained from patients were not exposed to any drug for at least 72 h (blank plasma), and were kindly supplied by health centre of Gorgan, Iran.

Instruments

We used a lab-made CL analyzer. The light emitted by the CL reaction was detected with no wavelength discrimination with a head on photomultiplier tube (PMT) located inside a darkroom. Reaction cell was a 0.50-cm path length quartz cell. The CL and fluorescence spectra were obtained with a spectrofluorimeter (Spectrolab, model Spectro-96), and UV-Vis spectra were obtained using a UV-Vis spectrophotometer (PG Instruments, model T90+).

Preparation of Samples

Plasma samples were obtained from healthy donors. One ml of the plasma sample was transferred into a centrifuge tube and 2.0 ml methanol was added for protein removal. The mixture was centrifuged at 4000 rpm for 20 min. The clear solution was transferred into a 25.0-ml volumetric flask and it was spiked with oxymorphone solution. Then, the mixture was diluted to mark with water. Final concentrations of oxymorphone were 0.0 (blank plasma), 67.6 ng ml^{-1}, 135.1 ng ml^{-1} and 337.8 ng ml^{-1}.

Standard addition protocol was also conducted for the determination of oxymorphone in plasma samples. It was assumed that the plasma samples are not containing oxymorphone. Therefore, five centrifuge tubes containing 1.0 ml plasma sample in each tube were spiked with oxymorphone standard solution for preparing oxymorphone containing plasma. Then, varying volumes of the standard solution of oxymorphone were added to the tubes. In the next step, 2.0 ml methanol was transferred into each centrifuge tube for protein removal. After centrifuging, the supernatant was transferred into a 10.0-ml volumetric flask and was diluted to the mark with water. Final concentration of oxymorphone was 33.8 ng ml^{-1}.

Synthetic samples were prepared to study the applicability of the method in pharmaceutical-like matrices. According to Endo Pharmaceuticals Inc. [44],

Table 1. Different Reagents Examined for the CL Determination of Oxymorphone

Reagent	Reagent concentration $\times 10^{-3}$ (M)	Description	CL Intensity (A.U.)[a]
$Ru(phen)_3^{2+}$-Ce(IV)-H_2SO_4	2.0-9.0-200[b]	A weak and broad peak (maximum at second 20s)	398
$Ru(phen)_3^{2+}$-MnO_4^--H_2SO_4	2.0-0.4-450[b]	A CL peak with two maximum: an intense sharp (maximum at second 0.5s) and a weak and broad peak (maximum at second 20s)	411
luminol-Na_2CO_3-H_2O_2	0.5-100-0.5	No significant difference was seen between the background and analyte signals	12400
Na_2SO_3- MnO_4^--H_2SO_4	50-1.0-100	A sharp and weak peak (maximum at second 0.2s)	3
MnO_4^--H_2SO_4	0.4-750[b]	A sharp and intense peak (maximum at second 0.6s)	2649
MnO_4^--polyphosphoric acid	6.0-750[b]	A sharp and intense peak (maximum at second 0.5s)	6450
Ce(IV)-H_2SO_4	10.0-100	No peak	1
$Na_2S_2O_8$	1.0	A weak and broad peak with a maximum at second 50	5
$NaIO_4$-NaOH	1.0-0.1	No peak	0

[a]In all experiments, 400 µl of first solution (luminol, $Ru(phen)_3^{2+}$, Na_2SO_3 or water) mixed with 400 µl oxymorphone (6.8 µg ml^{-1}) and then 200 µl of oxidizing agent (H_2O_2, Ce(IV)-H_2SO_4, $Na_2S_2O_8$, $NaIO_4$-NaOH or acidic permanganate) injected into the cell. [b]Optimum condition for the reagents.

oxymorphone injections (with trademark of OPANA) contain just sodium chloride, water and hydrochloric acid for adjusting pH. In OPANA injections the molar ratio of NaCl to oxymorphone is approximately 45. We prepared two more complex samples in which concentration of each substance was 100 times more than that of oxymorphone. Sample 1 was including lactose, NaCl, tartaric acid, glucose, carboxymethyl cellulose, sucrose and caffeine and sample 2 was including citric acid, $CaCl_2$, NaCl, Na_2SO_4, NH_4Cl, and sodium lauryl sulphite.

Analytical Procedure

Oxymorphone solution (800 µl) was transferred into the reaction cell using a calibrated sampler. Then, the cell was placed at its location in the darkroom and in front of photomultiplier tube (PMT). After a few seconds, 200 µl of acidic potassium permanganate solution was injected into the cell using a microsyringe and a needle. The time profile of CL emission was recorded by a computer. The data information was collected automatically into an Excel file.

RESULTS AND DISCUSSION

Chemiluminescence Reagents

Nine different reagents (as described in Table 1) were examined for the CL determination of oxymorphone. Recently we used luminol-H_2O_2 system for the determination of cysteine [25], $Ru(phen)_3^{2+}$-Ce(IV) system for the determination of Aspirin [45] and hydroxyzine [46] and permanganate-SO_3^{2-} for the determination of zolpidem [47]. The CL intensities were measured at the conditions mentioned in Table 1.

Among the CL systems studied for the determination of oxymorphone, direct oxidation by potassium permanganate was chosen for further investigations. Polyphosphoric acid produced a more intense CL emission than H_2SO_4. This result is in accordance with previous reports in which polyphosphoric acid produced greatest signal among other studied acids [48-50]. The reason might be due to the formation of protective cage-like structures around the excited Mn(II) emitter, which shift the wavelength of maximum emission from 734 ± 5 nm to 689 ± 5 nm and inhibit non-radiative relaxation pathways [28,51]

Optimization of Chemical Variables

To study the effect of chemical variables, influence of potassium permanganate and polyphosphoric acid on the CL intensity was investigated.

In most of the studies published, optimum concentration of potassium permanganate in CL reactions is reported around 1.0×10^{-3} M [21]. Therefore, the influence of concentration of potassium permanganate on the sensitivity was studied in the range of 1.0×10^{-4}-$1.0 \times$

10^{-1} M. These solutions were prepared using 0.1 M polyphosphoric acid. As seen in Fig. 2 the CL signal increases with increasing permanganate concentration to 6.0×10^{-3} M and then decreases. So, concentration of 6.0×10^{-3} M was selected as the optimum concentration of potassium permanganate.

The effect of polyphosphoric acid concentration on the CL intensity was studied in the range of 0.06-1.5 M. The CL response increased with increasing the concentration of polyphosphoric acid to 0.75 M and then decreased. Therefore, 0.75 M polyphosphoric acid was selected for further studies. The results are shown in Fig. 3.

Analytical Features

The CL reaction of oxymorphone in the system of acidic permanganate was very fast. The typical CL time profiles of oxymorphone are shown in Fig. 4. Maximum CL intensity is about 0.5 second from reagent mixing and then CL intensity is declined to base after about 3-5 s.

It was found that CL response of oxymorphone is linear for the concentration range of 13.5-337.8 ng ml^{-1} and 0.34-6.76 µg ml^{-1} with a limit of detection 3.5 ng ml^{-1} (signal to noise = 3). The sampling rate was 45 samples h^{-1} and the percentage of relative standard deviations (in 9 replicate measurements) were 3.1% and 3.6% for 135.1 ng ml^{-1} and 1.4 µg ml^{-1} oxymorphone, respectively.

Interference Study

The selectivity and direct application of the proposed method was studied by analyzing oxymorphone in the presence of some foreign species without any prior separation or isolation. The effect of these substances was determined by analyzing the standard solution of oxymorphone (338 ng ml^{-1}) in excess concentration of these compounds. The tolerance of each substance was taken as the largest amount yielding an error of less than 3σ in the CL intensity of 338 ng ml^{-1} oxymorphone (σ is the standard deviation in the response obtained from 11 times determination of 338 ng ml^{-1} oxymorphone). The results are shown in Table 2.

For comparing the CL intensity of oxymorphone with other narcotics or related drugs used in pharmaceutical formulations, twelve drugs were also investigated in the
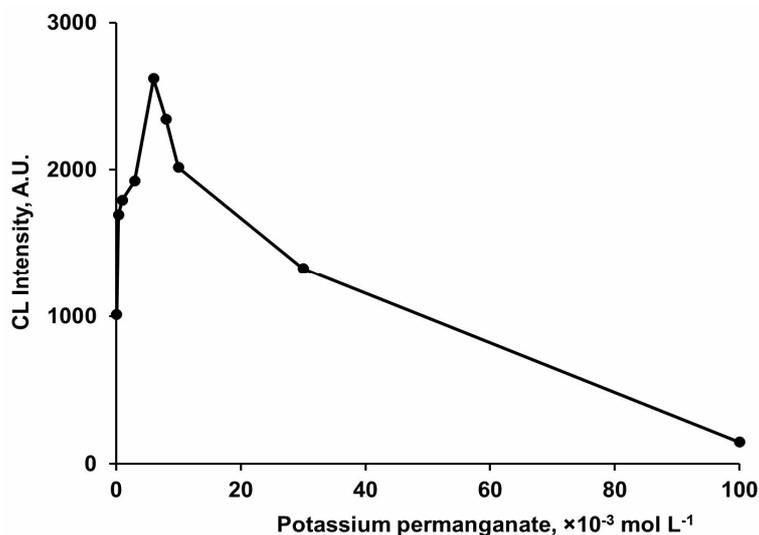
Fig. 2. Effect of permanganate concentration on the sensitivity. Conditions: polyphosphoric acid (0.1 M) and oxymorphone (6.8 µg ml^{-1}).
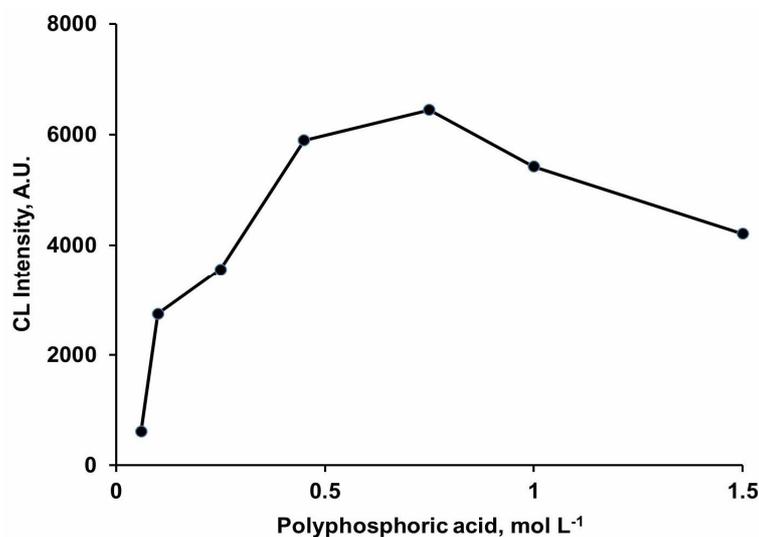

Fig. 3. Effect of polyphosphoric acid concentration on the CL intensity. Conditions: permanganate (6.0 × 10^{-3} M), oxymorphone (6.8 µg ml^{-1}).

CL system of acidic permanganate. In this study, concentration of each drug was 1.6×10^{-5} M. The results are shown in Table 3. CL time profiles for oxymorphone, buprenorphine, morphine and naltrexone in the system of potassium permanganate-polyphosphoric acid are compared in Fig. 5.

Application

The proposed CL method was used for the determination of oxymorphone in synthetic samples and
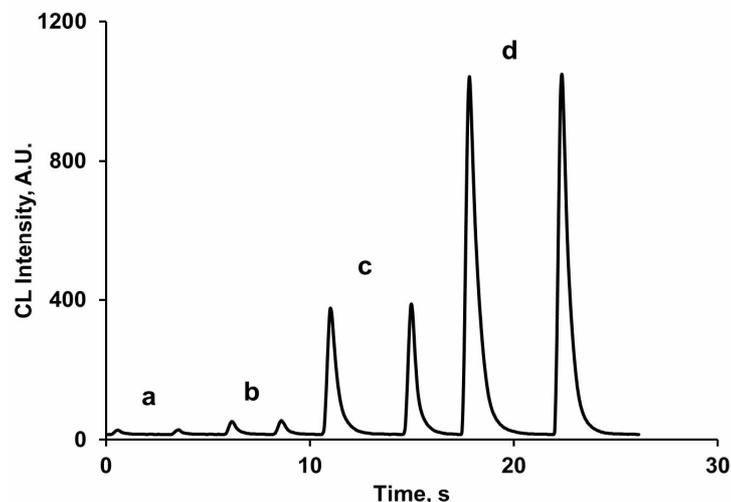
Fig. 4. Typical CL profiles for some concentrations of oxymorphone including: a) 67.6, b) 135.1 c) 675.6 and d) 1351.2 ng ml^{-1}.
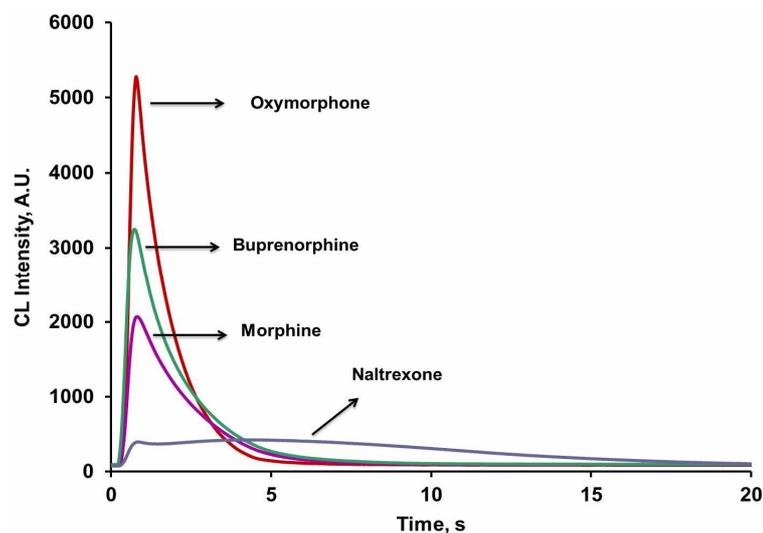

Fig. 5. CL time profiles for oxymorphone, buprenorphine, morphine and naltrexone in the system of potassium permanganate-polyphosphoric acid. Conditions: permanganate: 6.0×10^{-3} M, polyphosphoric acid: 0.75 M, concentration of each drug: 1.6×10^{-5} M.

plasma samples. We found that an oxymorphone free plasma prepared as described in experimental section does not have any CL emission with acidic permanganate and its response is like the blank (water) one. Tables 4 and 5 show the analytical recoveries from real samples.

Comparison between CL and Chromatographic Methods

In Table 6, some analytical characteristics are compared for the methods proposed for the determination of oxymorphone.

Table 2. Effect of Foreign Substances on the Determination of 338 ng ml^{-1} Oxymorphone

Substance	Substance to oxymorphone[a]
Benzoic acid, CaCl$_2$, Urea, Sucrose, Starch, Na$_2$SO$_4$, NH$_4$Cl, Lactose, Cafeine, Sodium lauryl sulphate, Sodium citrate, Carboxymethyl cellulose, Tartaric acid, Maleic acid, Glucose, Quinoline, Riboflavin, Carmoisine, Serine, Valine, Aspartic acid, Glycine, cystine, Methionine	100
Succinic acid, Uric acid, Ascorbic acid	10
Hydroquinone, Beta carotene, sodium oxalate, EDTA, Thiourea, Tryptophane	1
Salicylic acid	0.1

[a]Molar ratio of substance to oxymorphone.

Table 3 Relative CL Intensity of Oxymorphone Compare to some Alkaloids or Related Drugs

Drug	Relative CL Intensity[a]	Maximum intensity (A.U.)	Time of maximum intensity (s)
Oxymorphone	100	5195	0.5
Buprenorphine	58.8	3056	0.7
Morphine	38.1	1977	0.6
Naltrexone	6.2	321	4.2
Methadone	0.04	2	-
Oxycodone	0.04	2	-
Tramadol	0.04	2	-
Acetaminophen	0.02	1	-
Codeine	0	0	-
Dextromethorphan	0	0	-
Pholcodine	0	0	-
Thebaine	0	0	-
Diphenoxylate	0	0	-

[a]Concentrations of all substances were 1.6×10^{-5} M.

Table 4. Determination of Oxymorphone in Synthetic Samples

Concentration of oxymorphone ($\mu g\ ml^{-1}$)	Additives[a]	Found (n = 3) ($\mu g\ ml^{-1}$)	Recovery (%)
1.35	Lactose, NaCl, Tartaric acid, Glucose, Carboxymethyl cellulose, Sucrose, Caffeine	1.29±0.11	95.6
3.38	Citric acid, $CaCl_2$, NaCl, Na_2SO_4, NH_4Cl, Sodium lauryl sulphate	3.52±0.24	104.1

[a]Concentration for each additive was $1.0\times10^{-3}\ mol\ L^{-1}$.

Table 5. Determination of Oxymorphone in Plasma Samples

Sample	Added ($ng\ ml^{-1}$)	Found ($ng\ ml^{-1}$)[a]	Recovery (%)
Plasma 0	0.0	0.0	-
Plasma 1	67.6	63.4 ± 6.2	93.8
Plasma 2	135.1	128.1 ± 10.3	94.8
Plasma 3	337.8	344.2 ± 27.4	101.9
Plasma 4[b]	33.8	36.1[c]	106.8

[a]Mean values of three replications. [b]Determination was based on standard addition. [c]Without replication.

Most of the analytical methods proposed for the determination of oxymorphone are based on the chromatographic methods with mass spectrometry detection. These methods accompanied by sensitivity and chemical information for oxymorphone provide multianalyte information about related species, compounds and metabolites present in the sample. However, they are complex, time consuming, and they need expensive instrumentation. Some of them also use a pre-concentration method before the measurement [7,13]. Compared to these chromatographic methods, the CL method has the advantages of simplicity, rapidity and use of non-expensive instrumentation. CL methods have found extensive applications in many interesting areas, however their main disadvantages are generally related to their poor selectivity [52].

Mechanism

Some CL pathways might be proposed for the acidic permanganate-oxymorphone CL system, involving the formation of Mn(II)* species and oxidation products of oxymorphone in the excited state form [21]. To explore the CL mechanism, some experiments were performed and the results were compared with other published studies.

A red emission is visually observed when oxymorphone solution is mixed with acidic permanganate solution. Many researchers have also observed this red emission from the reactions with acidic potassium permanganate [53,54].

Table 6. Some Analytical Features of the Methods Proposed for the Determination of Oxymorphone

Method	LDR (ng ml^{-1})	LOD (ng ml^{-1})	Sample	Ref.
HPLC	10-750	2	urine	[7]
HPLC	1.0-8.9	Not reported	rat plasma	[8]
	8.9-178.4			
LC-MS/MS	0.1 to 100	Not reported	plasma	[9]
LC-MS/MS	0.2-250.0	Not reported	Plasma, urine	[10]
	10-5000			
LC-MS/MS	10-10000	5	plasma, urine	[11]
LC-MS/MS	1-100	0.8	plasma	[12]
SPE-LC-MS/MS	0.025-5.0	Not reported	plasma	[13]
LC–MS/MS	2-500	2	blood, liver	[14]
LC-MS/MS	0.05-10.0	0.03	plasma	[15]
LC-MS/MS	1-150 (pg mg^{-1})	1.2 (pg mg^{-1})	Hair	[16]
LC-MS/MS	1-511	0.1	rat plasma	[17]
LC-MS	0.5-250	Not reported	Ringer solution, rat plasma, rat brain tissue	[18]
GC-MS	25-2000	Not reported	urine	[19]
GC-MS	40-1600	20	urine	[20]
CL	13-337	3.5	Plasma, Synthetic injection	Present work
	337-6760			

The UV-Vis spectra of oxymorphone, its mixture with acidic potassium permanganate and also oxidation products (*i.e.* Mn^{2+} ions) are shown in Fig. 6. For oxymorphone, there are two absorption bands at 210 nm and 282 nm before addition of acidic potassium permanganate (see Fig. 6a). The characteristic absorption band at 210 nm is shifted toward red direction after addition of acidic potassium permanganate (Fig. 6d), at the same time, the absorption bands of potassium permanganate at 312 nm, 528 nm and 548 nm are disappeared (Fig. 6b). This indicates that the oxymorphone is oxidized by acidic potassium permanganate solution. The absorbance is highly increased in the range of 200-300 nm after addition of potassium permanganate to oxymorphone solution (see Fig. 6d). The reason might be due to production of Mn(II) ion which has a maximum absorption at 220 nm (see Fig. 6c) and also production of complexes between oxidizing products of oxymorphone and Mn(II) ions, because addition of Mn(II) solution to the mixture of
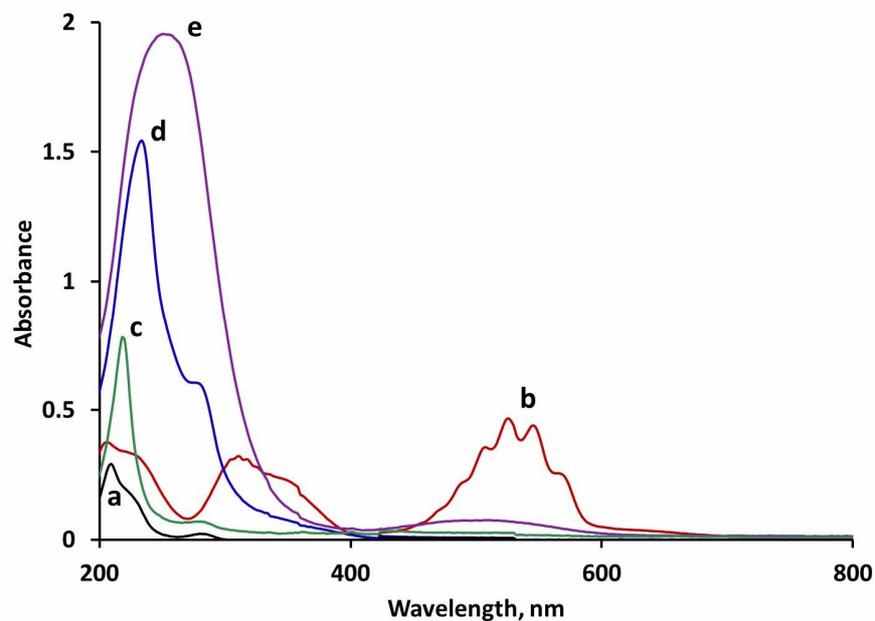
**Fig. 6.** UV-Vis spectrum of a) oxymorphone $(2.5 \times 10^{-5}$ M) b) potassium permanganate $(2.0 \times 10^{-4}$ M) in polyphosphoric acid $(2.5 \times 10^{-2}$ M) c) Mn^{2+} $(4.0 \times 10^{-3}$ M) d) mixture of oxymorphone-acidic potassium permanganate (concentrations as a and b) e) mixture of oxymorphone-acidic potassium permanganate (concentrations as a and b) and Mn^{2+} $(1.3 \times 10^{-3}$ M).
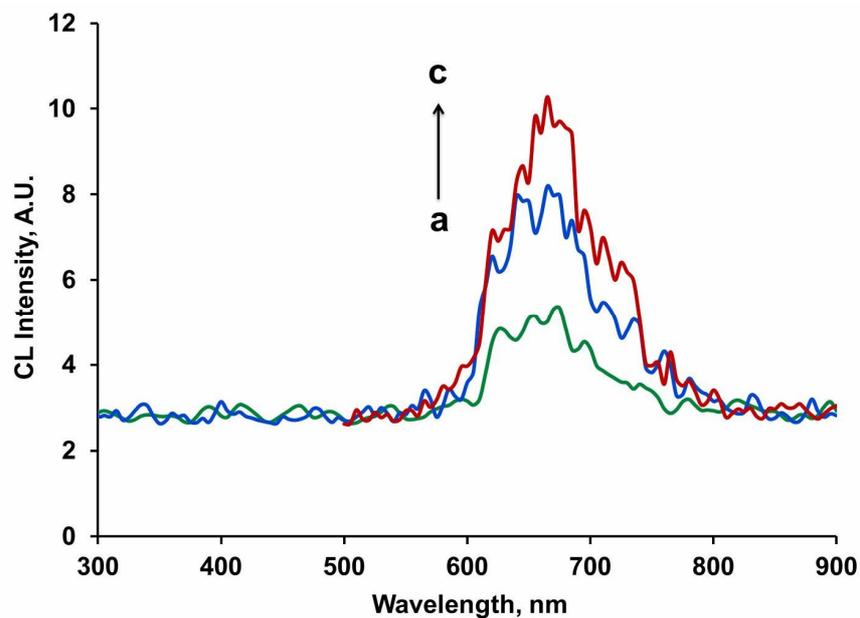

Fig. 7. CL spectrum of permanganate- polyphosphoric acid-oxymorphone. Conditions: 300 µl permanganate $(6.0 \times 10^{-3}$ M) in polyphosphoric acid (0.75 M) was injected to the cell including 2.0 ml oxymorphone a) 5.0×10^{-5} M, b) 1.0×10^{-4} M and c) 4.0×10^{-4} M).

oxymorphone and potassium permanganate increases the absorbance (see Fig. 6e).

Fluorescence spectra were obtained for oxymorphone and oxymorphone-permanganate mixture. Both spectra had the same peak maximum at 475 nm. The fluorescence spectrum of oxymorphone decreased after adding potassium permanganate. However, no new fluorescent peak was appeared and no shift in the maximum peak was observed.

No detectable CL intensity was obtained for oxymorphone with other oxidizing agents such as acidic Ce(IV) (see Table 1). This may suggest that the oxidation products of oxymorphone in exited state form are not the main emitters.

The CL reaction was very fast. Therefore, a fast scan (15000 nm min^{-1}) using batch mode was used for taking CL spectrum. Figure 7 shows the CL spectra for three different concentrations of oxymorphone. In all CL spectra, there is a single broad band between 600-750 nm. Many researchers have also reported this broad band and ascribed it to the Mn(II)* product of the reaction [51, 55-59]. This claim has been recently confirmed by Adcock *et al*. [60]. They compared the laser-induced photoluminescence of Mn(II) with CL from the reaction between acidic potassium permanganate and sodium borohydride and found that red CL emission from potassium permanganate reactions emanates from an electronically excited Mn(II) species. Moreover, Slezak *et al*. [61] found that the Mn(II)* species can be generated when Mn(III) reacts with radical intermediates derived from the analyte.

According to the above discussion, the following mechanism is proposed for the CL reaction of oxymorphone with acidic permanganate.

$$MnO_4^- + Oxymorphone \rightarrow Mn(III) + Radical\ intermediates$$

$$Mn(III) + Radical\ intermediates \rightarrow Mn(II)^* + Other\ products$$

$$Mn(II)^* \rightarrow Mn(II) + h\nu\ (600-750\ nm)$$
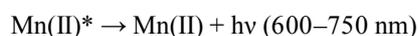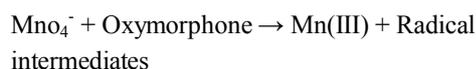
CONCLUSIONS

It has been found that oxymorphone can produce intense CL in the reaction with acidic potassium permanganate, and the CL intensity is enhanced in polyphosphoric acid. Accordingly, a direct CL method has been developed for determination of oxymorphone. This method is simple and less expensive compared to the existing techniques for the determination of oxymorphone. The mechanism investigation showed that the Mn(II)* species are luminophor. This method has been used for the determination of oxymorphone in the synthetic samples and human plasma.

ACKNOWLEDGMENTS

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