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# Determination of naltrexone based on its enhancement effect in the chemiluminescence reaction of Ru $(phen)_3^{2+}$ with acidic cerium(IV)

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**ABSTRACT**

*This work establishes a simple method for the determination of naltrexone by chemiluminescence (CL) technique. This method is based on the enhancement effect of naltrexone on the weak CL emission raised from reaction between tris(1,10 phenanthroline)ruthenium(II), $Ru(phen)_3^{2+}$, and cerium(IV) (Ce(IV)). Under the optimum chemical conditions, CL intensity was correlated linearly with concentration of naltrexone in the range of 0.07-13.7 µg $mL^{-1}$ with a correlation coefficient of 0.9990. The detection limit for this drug was calculated 0.06 µg $mL^{-1}$ (3:1 signal-to-noise ratio) and the relative standard deviation for 10 repetitive determinations of 1.37 µg $mL^{-1}$ naltrexone was 5.3 %. The method was applied to the determination of naltrexone in human plasma and the results were in good agreement with the spiked values.*

**Keywords:** Chemiluminescence, Naltrexone, Time resolve, Plasma

## INTRODUCTION

Opioid antagonists are drugs that block some or all opioid receptor subtypes. Naltrexone (17-cyclopropylmethylmethyl-6-deoxy-7, 8-dihydro-14-hydroxy-6-oxo-17-normorphine) (figure 1) a pure opioid antagonist, is a synthetic congener of oxymorphone with no opioid agonist properties. Naltrexone is used to treat alcohol dependence and opioid dependence and used as a respirator stimulant to treat opioid dependence. It is used for opioid blockade therapy of post-addicts and used to treat intoxication as well as maintenance therapy due to long duration of action. To treat alcohol dependence, it prevents relapse of alcoholism, reduce alcohol craving and number of drinking days [1-3].

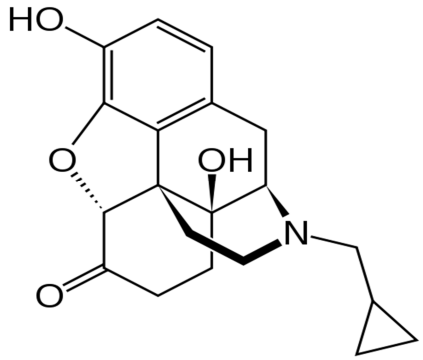


**Figure 1 Chemical structure of naltrexone**

A variety of analytical techniques proposed for the determination of naltrexone, including high performance liquid chromatography [4-6], liquid chromatography (LC) [7, 8], gas chromatography-mass spectrometry (MS) [9, 10], LC-MS [11] and spectrofluorimetry [12].

Chemiluminescence (CL) methods because of their intrinsic advantages, such as high sensitivity, wide linear dynamic range and simple instrumentation have become an important and valuable detection method in analytical chemistry [13, 14]. Beginning with the observations of Hercules and Lytle in 1966 [15], CL reactions with ruthenium(II) complexes such as tris(2,2-bipyridyl)-ruthenium(II), $Ru(bpy)_3^{2+}$, and tris(1,10-phenanthroline)-ruthenium(II), $Ru(phen)_3^{2+}$, have been extensively studied and exploited for a wide variety of analytical applications [16-20]. Compared to $Ru(bpy)_3^{2+}$, $Ru(phen)_3^{2+}$ has been reported to produce more intense CL and electrochemiluminescence (ECL) in aqueous solutions [21-24]. Only one CL method has been reported for the determination of naltrexone up to now. Campiglio [25] proposed a CL method for the determination of naltrexone based on direct oxidation of naltrexone by potassium permanganate. In his method, LDR and LOD were reported 0.05-1.00 and 0.025 µg $mL^{-1}$, respectively.

Developing new CL methods for analysis of pharmaceuticals is important because of some problems that may limit the application of some CL systems. Firstly, a CL reagent is not always limited to just one unique analyte that leads to interference effects in methods without a separation stage. Type and extent of interferences is different in each CL system [26]. Another problem is the dependence of the CL emission on several environmental factors such as temperature, solvent, ionic strength, pH, and other species present in the system which should be dealt with during HPLC or capillary electrophoretic separation procedures as well as during flow injection analysis (FIA) [27-29]. Hence, one CL procedure may be appropriate but another may not be suitable for coupling with a separation method.

In this work, it is found that the weak CL emission intensity in the system of $Ru(phen)_3^{2+}$-Ce(IV) was enhanced in the presence of naltrexone. The proposed method was successfully used for the quantification of naltrexone in human plasma samples. The broad time profiles of naltrexone in this CL system provide the benefit of time resolve CL to reduce the effect of blank interference from plasma matrix.

## EXPERIMENTAL SECTION

### Chemicals and reagents

All solutions were prepared by using reagent grade materials in doubly distilled water. Standard solution of naltrexone (340.0 µg $mL^{-1}$, $1.0\times10^{-3}$ mol $L^{-1}$) was prepared by dissolving 0.034 g of naltrexone (Temad Co., Iran) in water and diluting to 100.0 ml. Working standard solutions were prepared by appropriate dilution of this stock solution. Standard solution of $Ru(phen)_3^{2+}$ (0.01 mol $L^{-1}$) was prepared by dissolving 0.3640 g of dichlorotris(1,10-phenanthroline)ruthenium(II) hydrate (Sigma-Aldrich, Germany) with water in a 50.0-mL volumetric flask. To prepare each Ce(IV) solution with concentration between $1.0\times10^{-3}$ and $1.8\times10^{-2}$ mol $L^{-1}$, calculated amount of ceric ammonium nitrate (Riedel-de Haën, Germany) was dissolved in proper volume of $H_2SO_4$ solution (1.0 mol $L^{-1}$) and then the solution was further diluted with distilled water in a 100.0-mL volumetric flask. Finally, concentration of $H_2SO_4$ in the Ce(IV) solutions was between 0.04 and 0.90 mol $L^{-1}$. Methanol (Dr Mojallali Co., Iran) was used for protein precipitation. Plasma from patients not exposed to any drug for at least 72 h (blank plasma) was kindly supplied by health center of Gorgan, Iran.

### Preparation of plasma samples

Methanol was added to plasma samples for deproteination. One mL methanol was added to 1.0 mL of plasma in a centrifuge tube. Then the mixer centrifuged at 6000 rpm for 15 min. The protein-free supernatant was transferred into a 25.0-mL volumetric flask. Then, calculated volume of standard solution of naltrexone was added into the flask for spiking and then the mixture was diluted to 25.0 mL with distilled water.

### Apparatus

In this study we used a laboratory built CL analyzer with a head on photomultiplier tube (PMT). The emitted light by the CL reaction was detected by the PMT (Hamamatsu, model $R_{329}$) with no wavelength discrimination and recorded by a computer. The PMT was operated at 1200 V, provided by a stable power supply. Reaction cell was a 0.50-cm path length quartz cell. The block diagram of the instrument is shown in figure 2.

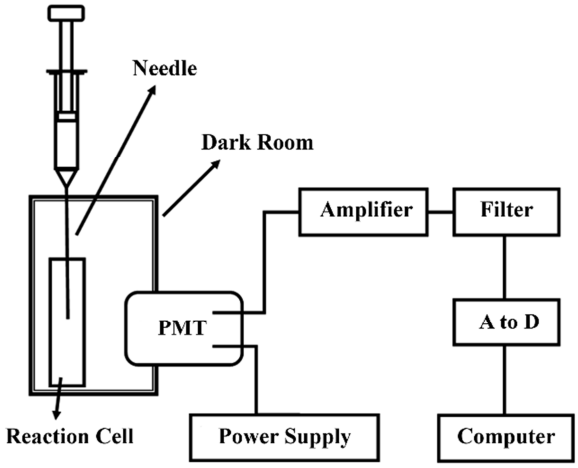


**Figure 2 Schematic block diagram of the CL instrument. PMT: photomultiplier tube; A to D: Analogue-to-digital converter**

**General Procedure**

An aliquot (400 µL) of naltrexone solution along with 400 µL of $2.0\times10^{-3}$ mol $L^{-1}$ of $Ru(phen)_3^{2+}$ were transferred into the reaction cell and the cell was positioned into the cell holder, in front of PMT. Then the program was started. After a few seconds, 200 µL of acidic Ce(IV) was injected into the cell by a microsyringe. The full CL intensity vs. time was recorded and all of these data information were automatically collected into an Excel file.

## RESULTS AND DISCUSSION

**CL response**

In this work, it is found that the weak CL emission intensity in the CL system of $Ru(phen)_3^{2+}$-Ce(IV) is remarkably enhance in the presence of naltrexone. CL profiles of naltrexone illustrated that the CL reaction was slow. It lasts for 4.2 seconds to get to the maximum peak, compared with 40-50 seconds for the signal to decrease to the base. In this research, height of each CL peak at $10^{th}$ second after injection of Ce(IV) solution, have been chosen as analytical signal. Typical CL profiles of naltrexone are shown in figure 3.

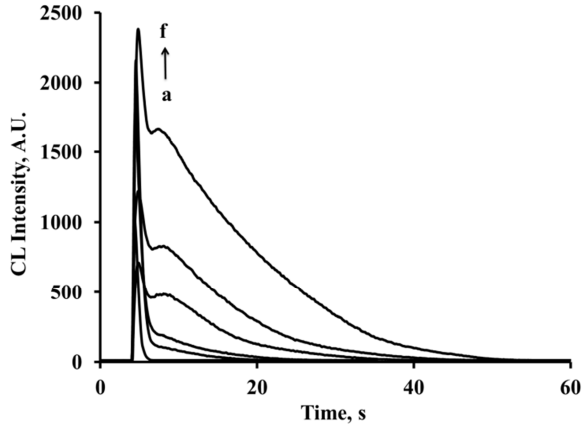


**Figure 3 Typical CL time profiles for some concentrations of naltrexone including: a) blank, b) 0.68, c) 1.37 d) 3.41 e) 6.83 f) 13.66 µg $mL^{-1}$**

As shown in figure 3, there are two peaks in the CL time profiles of naltrexone. The first peak at second 0.9 is due to background emission from reaction between $Ru(phen)_3^{2+}$ and Ce(IV). The first peak is the same for the blank solution (figure 3a) and the sample solutions containing naltrexone (figure 3b to 3f). The second peak at second 4.2s after starting the CL reaction is related to naltrexone. In this study, CL intensity at second 10 after injection of Ce(IV) has been selected as analytical signal to reduce the effect of some blank interferences in plasma samples.

**Optimization of Chemical Variables**

In this research, a series of experiments was conducted to establish the optimum conditions for the determination of naltrexone. The optimized parameters were $Ru(phen)_3^{2+}$, Ce(IV), and $H_2SO_4$ concentrations. Ce(IV) is not soluble in water, but becomes stable and soluble when sulfuric acid is added. So,The effect of sulfuric acid concentration on the CL emission was examined over the range 0.04-0.9 mol $L^{-1}$ in presence of $5.0\times10^{-3}$ mol $L^{-1}$ Ce(IV) and $2.0\times10^{-3}$ mol $L^{-1}$ $Ru(phen)_3^{2+}$. As can be seen in figure 4, the highest response was obtained with 0.15 mol $L^{-1}$ $H_2SO_4$.

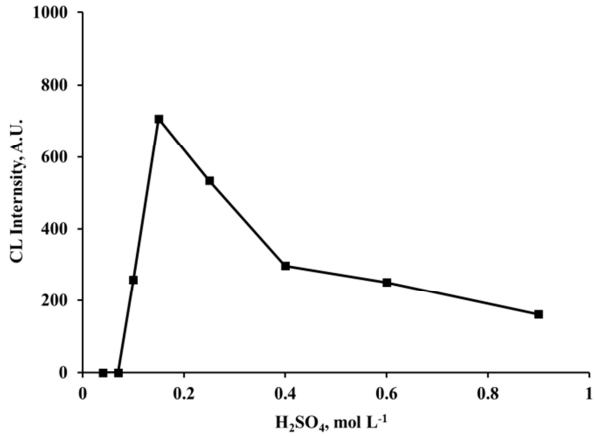


**Figure 4 Optimization of $H_2SO_4$ concentration**
*Conditions: naltrexone 8.2 μg $mL^{-1}$ $Ru(phen)_3^{2+}$ ($2.0\times10^{-3}$ mol $L^{-1}$), Ce(IV) ($5.0\times10^{-3}$ mol $L^{-1}$)*

Under the optimum conditions noted above, the effect of $Ru(phen)_3^{2+}$concentration was examined in the range (0.5-6.0)$\times10^{-3}$ mol $L^{-1}$. Figure 5 shows that $3.0\times10^{-3}$ mol $L^{-1}$ of $Ru(phen)_3^{2+}$ gave the greatest CL intensity.

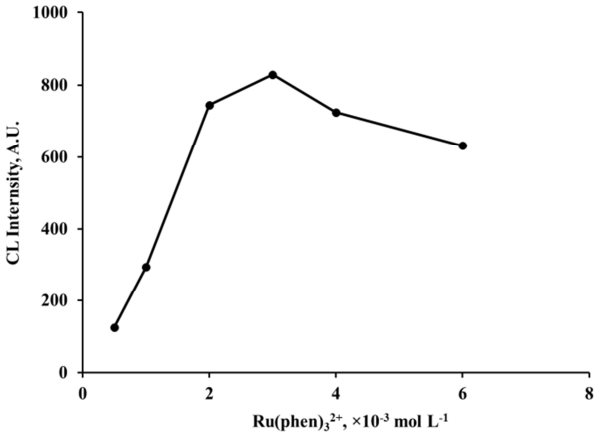


**Figure 5 Optimization of $Ru(phen)_3^{2+}$ concentration**
*Conditions: naltrexone 8.2 μg $mL^{-1}$, $H_2SO_4$ (0.15 mol $L^{-1}$), Ce(IV) ($5.0\times10^{-3}$ mol $L^{-1}$).*

The Effect of Ce(IV) concentration upon the CL intensity in presence of 0.15 mol $L^{-1}$ $H_2SO_4$, and $3.0\times10^{-3}$ mol $L^{-1}$ $Ru(phen)_3^{2+}$ was examined in the range $1.0\times10^{-3}$-$1.8\times10^{-2}$ mol $L^{-1}$ (figure 6). The maximum CL intensity was obtained with $1.0\times10^{-2}$ mol $L^{-1}$ Ce(IV).

**Analytical parameters**

The CL response was linear with concentration of naltrexone in the range 0.07-13.7 μg $mL^{-1}$ with a correlation coefficient of 0.9990. LOD was calculated 0.06 μg $mL^{-1}$ (3:1 signal-to-noise ratio). Reproducibility was investigated and the relative standard deviation for 10 repetitive determinations of 1.37 μg $mL^{-1}$ naltrexone solution was 5.3%.

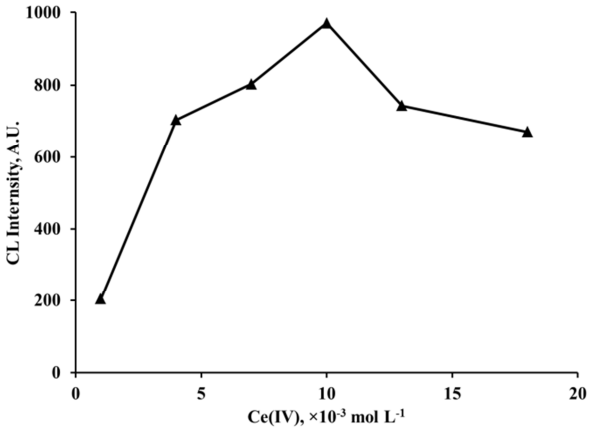


**Figure 6 Optimization of Ce(IV) concentration**
*Conditions: naltrexone 8.2 μg mL$^{-1}$, $H_2SO_4$ (0.15 mol L$^{-1}$), $Ru(phen)_3^{2+}$ ($3.0\times10^{-3}$ mol L$^{-1}$).*

**Interference Study**

The selectivity and the possible analytical applications of the proposed CL method have been studied by analyzing naltrexone in presence of some ions, excipients used in pharmaceutical preparations and amino acids without any prior separation or isolation. The effect of each foreign species on the CL intensity was investigated by determining the CL emission of the synthetic sample solutions containing 1.37 μg mL$^{-1}$ of naltrexone and various amounts of each excipient. The tolerance limit of each substance was taken as the amount which caused an error of less than 3σ in the analytical signal of 1.37 μg mL$^{-1}$ of naltrexone (σ is the standard deviation of response obtained from 10 times repeating determination of 1.37 μg mL$^{-1}$ naltrexone). The results are shown in Table1.

**Table 1 Effect of foreign substances on the measurement of 1.37 μg mL$^{-1}$ naltrexone**

| Substance | [a] Substance to naltrexone |
|---|---|
| Saccharin, Sodium lauryl sulphite (SLS), Starch, Thiourea, Glucose, Benzoic acid, Serine, Cystine, Lactose, Valine, Threonine, $Cu^{2+}$, $SO_4^{2-}$ | 500 |
| Salicylic acid, maleic acid, EDTA, Urea, $Ca^{2+}$, $NH_4^+$, $Cl^-$, Proline, Alanine, Glycine | 50 |
| Quinoline, Riboflavin, Caffeine, Cysteine | 10 |
| Ascorbic acid, Tartaric acid, Citric acid, Oxalic acid | 1 |

[a] *Molar ratio of substance to naltrexone*

In this CL system, protein free plasma has a sharp peak with a maximum at 0.9 seconds after injection of Ce(IV) solution and its CL response has a fast decline to baseline after about 10 seconds. So, to reduce the effect of blank interferences from human plasma, CL intensity at 10 seconds after injection of Ce(IV) solution is selected as the analytical signal for interference and application studies.

Compounds with a tertiary amine or carboxylic acid group, and also some ions can enhance the CL intensity in the reaction among $Ru(phen)_3^{2+}$ and an oxidizing agents [30-33]. The CL time profiles for many of the investigated compounds in Table 1 are somehow sharp, so that, their CL intensities are approximately equal to zero (or it is very little) at 10 s after starting CL reaction. Consequently, they have little or zero blank interference for the determination of naltrexone that have a broad CL time profile with a detectable response at 10 seconds after injection of Ce(IV) solution.

**Application**

The proposed method has been used for the quantification of naltrexone in human plasma samples.

The time resolved CL approach was used to reduce the effect of some blank interferences in plasma samples. It was found that a naltrexone free plasma sample prepared according to the procedure described in experimental section has a sharp CL time profile with maximum peak at 0.9 s after injection of Ce(IV) solution. CL intensity of blank plasma sample decreases rapidly to baseline after about 10 s. In this CL system naltrexone has a wide time profile with a detectable intensity which is high enough until 20 seconds after injection of Ce(IV) solution. Therefore, in order to reduce the effect of blank interferences in plasma samples, CL intensity at 10 s after injection of Ce(IV) solution was chosen as analytical signal in application studies. By this way, analytical signal could be free of blank interferences caused by some substances such as ascorbic acid and cysteine in human plasma. We used this strategy

successfully for determination of carminic acid [34], ketotifen [35], aspirin [36], and recently, mepivacaine and hydroxyzine in real samples. Table 2 shows the analytical recoveries from plasma samples.

**Table 2 Determination of naltrexone in plasma samples**

| Added (µg $mL^{-1}$) | Found (µg $mL^{-1}$) [a] | Recovery (%) |
|---|---|---|
| 0.00 | 0.02±0.02 | - |
| 0.14 | 0.16±0.02 | 114.3 |
| 1.09 | 1.17±0.08 | 107.3 |
| 5.46 | 5.29±0.32 | 96.9 |
| 10.92 | 11.34±0.63 | 103.8 |

[a] *Mean values of three replications*

**Possible CL mechanism**

In this CL system, the detection chemistry generally relies upon two key steps. Firstly, chemical or electrochemical oxidation of $Ru(phen)_3^{2+}$ yields $Ru(phen)_3^{3+}$. Secondly, this complex is reduced by an appropriate analyte (or analyte oxidation product) to produce an electronically excited $[Ru(phen)_3^{2+}]^*$, which can return to the ground state by the emission of light. This CL matches the characteristic photoluminescence of $Ru(phen)_3^{2+}$, where a short-lived triplet state is generated by promotion of an electron from the $t_{2g}d^6$ orbital on the metal to the π* antibonding orbital (a metal-ligand charge transfer; MLCT) [37].

The color of $Ru(phen)_3^{2+}$ solution changes from orange to green immediate after oxidation with Ce(IV) solution and production of $Ru(phen)_3^{3+}$ [38, 39]. Then, the color of the mixture changes slowly from green to orange. UV-Vis spectrum of $Ru(phen)_3^{2+}$ (spectrum a) and the mixture of $Ru(phen)_3^{2+}$-Ce(IV) with one-min interval times (spectrum b to g) are shown in figure 7.

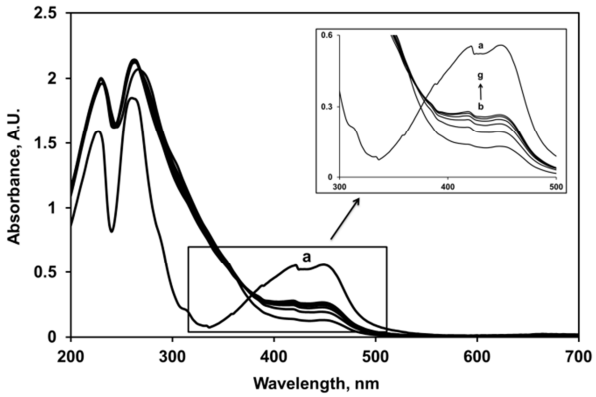


**Figure 7 UV-Vis spectrum of a) $Ru(phen)_3^{2+}$ ($5.0\times10^{-5}$mol $L^{-1}$), b to g) 2.0 mL $Ru(phen)_3^{2+}$ ($5.0\times10^{-5}$mol $L^{-1}$) and 1.0 mL Ce(IV) ($7.0\times10^{-4}$mol $L^{-1}$ in 0.014 mol $L^{-1}$ of $H_2SO_4$)**

The absorbance in the range of 400 to 500 nm (spectrum a) is related to $Ru(phen)_3^{2+}$ complex. Absorbance in this region decreases immediately after mixing the $Ru(phen)_3^{2+}$ solution with Ce(IV) solution (spectrum b) and then it increases slowly to its equilibrium value (spectrum c to g). Because, the resulting $Ru(phen)_3^{3+}$ complex produced in the oxidation reaction, is a powerful oxidant and it can oxidize water to protons and $O_2$ molecules [40]. Therefore, $Ru(phen)_3^{3+}$ complex returns slowly to its reduced state, $Ru(phen)_3^{2+}$. Reducing agents can reduce $Ru(phen)_3^{3+}$ very fast. Electrons can transfer from the reducing agent to the π*-orbital of phenanthroline ligands and the excited form of $Ru(phen)_3^{2+}$ which is the same as π* metal-to-ligand charge transfer (MLCT) state could be produced [41]. The excited electron in the π* orbital then undergoes intersystem crossing to the lowest triplet state of $Ru(phen)_3^{2+}$, from where emission occurs [42].

In order to confirm the above mentioned mechanism, some CL pathways might be investigated for the $Ru(phen)_3^{2+}$-Ce(IV)-naltrexone CL system, involving formation of excited Ce(III) [43] oxidation products in excited states and excited form of $Ru(phen)_3^{2+}$, $[Ru(phen)_3^{2+}]^*$ [44].

No detectable CL intensity recorded for the mixture of Ce(IV)-naltrexone. This suggests, that oxidation products and excited Ce(III) are not main CL emitters. The CL spectrum was scanned with a spectrofluorimeter (Spectrolab, model Spectro-96) using batch mode, a fast scan (15000 nm $min^{-1}$) and with turned off excitation lamp. The CL spectra were acquired as shown in figure 8 for $Ru(phen)_3^{2+}$-Ce(IV) (spectrum a), and $Ru(phen)_3^{2+}$-Ce(IV)-naltrexone (spectrum b).

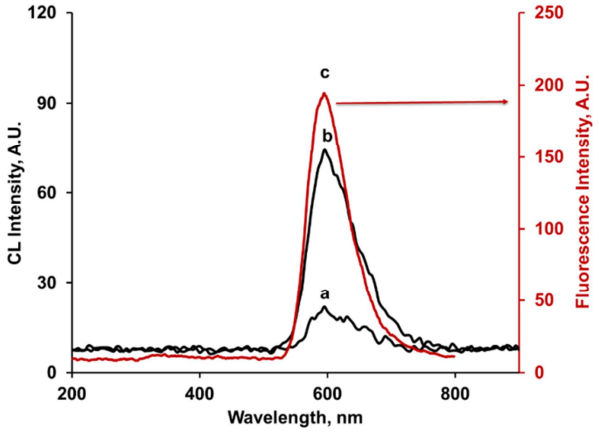


**Figure 8 CL spectra of a) $Ru(phen)_3^{2+}$-Ce(IV) b) $Ru(phen)_3^{2+}$-Ce(IV)-naltrexone c) fluorescence emission ($\lambda_{ex}$= 325 nm) of $Ru(phen)_3^{2+}$.**
*Conditions: 200 µL naltrexone (34.14 µg $mL^{-1}$), 1 mL $Ru(phen)_3^{2+}$ ($3.0\times10^{-3}$ mol $L^{-1}$), 0.5 mL Ce(IV) ($1.0\times10^{-2}$ mol $L^{-1}$ in 0.1 mol $L^{-1}$ of $H_2SO_4$).*

It could be clearly indicated that the maximum emissions for both mixtures (a and b) are ~595 nm which is same as maximum fluorescence emission ($\lambda_{ex}$= 325 nm) of $Ru(phen)_3^{2+}$ at 595 nm (spectrum c). This indicated that the CL spectra were independent of naltrexone and the emitter is $Ru(phen)_3^{2+}$.

naltrexone is a tertiary amine and from previous studies, the oxidation of tertiary amines is understood to produce a short-lived radical cation. The α-carbon is then deprotonated, yielding a strongly reducing intermediate. This reduces the $Ru(phen)_3^{3+}$ (produced by oxidant) to the excited state that subsequently emits light [45-48].

According to the above discussion, following mechanism proposed for the CL reaction of naltrexone.

$Ru(phen)_3^{2+} + Ce(IV) \rightarrow Ce(III) + Ru(phen)_3^{3+}$ (1)
$Hyd + Ce(IV) \rightarrow Ce(III) + naltrexone^{+\bullet}$ (2)
$naltrexone^{+\bullet} \rightarrow naltrexone^{\bullet} + H^+$ (3)
$Ru(phen)_3^{3+} + naltrexone^{\bullet} + H_2O \rightarrow [Ru(phen)_3^{2+}]^* +$ naltrexone fragments (4)
$[Ru(phen)_3^{2+}]^* \rightarrow Ru(phen)_3^{2+} + h\upsilon$ (595 nm) (5)

## CONCLUSION

The proposed method is a new CL reaction for the determination of naltrexone. The method is based on the enhancement effect of naltrexone on the CL reaction of $Ru(phen)_3^{2+}$ with acidic Ce(IV). The broad time profile of naltrexone allowed us to reduce the effect of some interfering substances such as ascorbic acid and cysteine in plasma samples. Therefore, the method is simple for the determination of naltrexone in human plasma.

**Acknowledgements**
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