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Determination of Remifentanil in Pharmaceuticals Using Chemiluminescence System of $Ru(phen)_3^{2+}$-Ce(IV)

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In this study, new chemiluminescence (CL) method was proposed to determine the amount of remifentanil in pharmaceuticals. We found that the weak CL intensity in the reaction between acidic cerium(IV) and $Ru(phen)_3^{2+}$ complex increases significantly in the presence of remifentanil. Effect of remifentanil was investigated in some other CL systems such as luminol-IO_4^-, direct oxidation using acidic cerium(IV) or acidic $KMnO_4$. Moreover, the effect of different dyes as a sensitizer was investigated in the $KMnO_4$-Dye CL system. The dyes used in this study were crystal violet, amido black, naphthol green, amaranth, rhodamine 6G, safranin, orange G, fluorescein, and chromotrope 2R. The results showed that remifentanil has the highest CL intensity and S/B ratio in the acidic cerium(IV)-$Ru(phen)_3^{2+}$CL system. The reaction mechanism was evaluated by studying the CL reaction kinetics in the presence and absence of remifentanil and spectrophotometric spectra. The results indicate that remifentanil can convert $Ru(phen)_3^{3+}$ complex rapidly to $Ru(phen)_3^{2+*}$ complex, which emits light when it returns to its ground-state. The method's linear dynamic range, detection limit, and reproducibility for four repetitive measurements of 109.39 μg ml^{-1} were 1.75-145.85, 1.41 μg ml^{-1}, and 2.3%, respectively. The method proposed in this study was used to determine the content of remifentanil in pharmaceutical preparations.

Keywords: Remifentanil, Chemiluminescence, $Ru(phen)_3^{2+}$, Pharmaceuticals

INTRODUCTION

Remifentanil (methyl-1-(3-methoxy-3-oxopropyl)-4-(N-propanoylanilino) piperidine-4-carboxylate) is available under the brand names of Ultvia and Remifentanil in pharmacies and hospitals. Remifentanil with the structural formula of $C_{20}H_{28}N_2O_5$ is shown in Fig. 1.

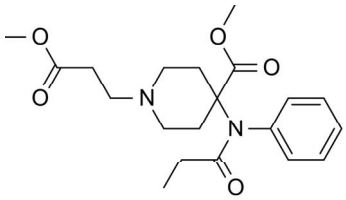

Fig. 1. Chemical structure of remifentanil.

Remifentanil is a synthetic narcotic drug derived from fentanyl, used as a surgical anaesthetic in a wide range of patients, including adults and children. It has a short-term effect and a short half-life because it is rapidly inactivated by blood and tissue esterases. Remifentanil is used as a sedative, analgesic, hypnotic, and anaesthetic. This drug is used to maintain anaesthesia during surgery and as a potent analgesic after surgery. Remifentanil is also used during spinal surgery [1], heart surgery, and gastric bypass surgery [2]. Recent studies have also shown that remifentanil has an antitussive effect when awakened from anaesthesia due to the placement of a tube for surgery [3]. In general, remifentanil is very suitable for cases that require complete analgesia for a limited time. The effect of remifentanil is enhanced by drugs such as antihypertensives, anxiolytics, and hypnotics [4-6]. Remifentanil is soluble in water, methanol, and ethyl acetate and is available in solid powder form in 3, 5, and 10 ml vials, each containing 1.0, 2.0, and

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5.0 mg, respectively used for intravenous injection [7].

Several chromatographic methods were published for the determination of remifentanil in drug and blood samples, such as liquid chromatography-mass spectrometry (LC-MS) [8-13], high-performance liquid chromatography (HPLC) [14-17], and gas chromatography [18,19].

All the methods proposed to determine remifentanil are based on inherently complex and expensive chromatographic separations. Therefore, it is vital to suggest fast and straightforward methods for determining the amount of remifentanil in pharmaceuticals. Chemiluminescence (CL) is a chemical phenomenon in which rays of photons are produced as a product during a chemical reaction, resulting in visible glow and light during the reaction. The CL reaction rate is a function of the concentration of the chemicals, so CL methods are suitable for quantitative analysis. CL is a sensitive analytical method that has been widely used in many fields, such as the analysis of pharmaceuticals, organic, inorganic, and biological samples [20-22].

The CL intensity can be represented by the equation $I_{CL} = \Phi_{CL}$ (-dA/dt). In this equation, I_{CL} is the intensity of CL (photons per second), Φ_{CL} is the quantum efficiency of the CL reaction as the number of photons emitted per number of reacted molecules [23]. The quantum efficiency of CL for most reactions used in analytical chemistry is between 0.01 and 0.2. Tris (2, '2-bipyridyl)ruthenium(II) ($(Ru(bipy)_3^{2+}$) and tris (1,10-phenanthroline)ruthenium(II) ($Ru(phen)_3^{2+}$) are complexes with high quantum efficiency that have many applications in CL investigations [24-27].

In this study, a new CL method has been proposed to determine the amount of remifentanil in pharmaceuticals. The method is based on the weak CL intensity in the reaction between acidic cerium(IV) and $Ru(phen)_3^{2+}$ complex increases significantly in the presence of remifentanil.

EXPERIMENTAL

Chemicals and Solutions

Materials and reagents with analytical grade were used without any purification. 20.0 mg of pure powder solid (Remifentanil hydrochloride, Aburaihan Co, Iran) was weighed and transferred into a 100.0 ml volumetric flask, and then the flask was filled with deionized water to prepare a solution with a remifentanil concentration of 182.3 ppm (4.8×10^{-4} M). Other concentrations of remifentanil solution were prepared by serial dilution.

To prepare acidic cerium(IV) solution with a particular concentration, first, the calculated amount of cerium ammonium nitrate salt (ChemLab, Belgium) is weighed and transferred to a 100.0 ml volumetric flask, and then the appropriate volume of 1.0 M of sulfuric acid was added to the flask. The volume was adjusted to the mark with deionized water. The prepared acidic cerium(IV) solution is stable; however, it was kept in the dark for 24 h to stabilize the concentration. 0.0180 g of dichlorotris(1,10-phenanthroline)ruthenium(II) hydrate (Sigma-Aldrich, Germany) was weighed and transferred to a 25.0 ml volumetric flask and then dissolved using deionized water to prepare a solution of ($Ru(phen)_3^{2+}$) complex with a concentration of 1.0×10^{-3} M.

Preparation of Remifentanil Ampoules

The contents of 1 vial of 2.0 mg of the drug were transferred to a 25.0 ml volumetric flask and then diluted to the mark by deionized water to prepare the ampoule sample. The approximate concentration of remifentanil in this solution is within the linear range of the calibration curve.

CL Instrument

The CL device consists of a reaction cell (1.0 cm width) inside a dark room. This cell is located directly in front of the photomultiplier tube detector (PMT, FEU-85, Russia) to detect the light produced by the CL reaction. The PMT was connected to a high voltage power supply (up to 1250 volts). The current generated in the PMT is converted to a voltage by an electric current to voltage amplifier. The voltage using a 16-bit analogue-to-digital converter was transmitted to a PC and displayed as a function of time (with 20 ms intervals) and was recorded in an Excel file. The schematic diagram of the CL instrument is shown in Fig. 2.

Analytical Procedure

To obtain the CL response of the blank (B) or the sample (S), 400 µl of deionized water or remifentanil sample solution along with 400 µl of $Ru(phen)_3^{2+}$ solution

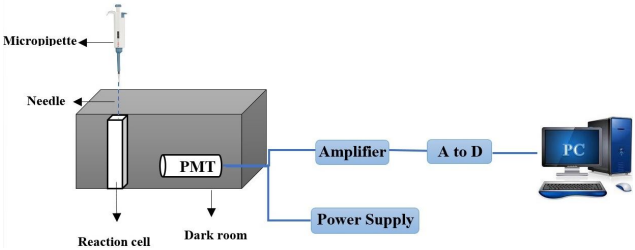

Fig. 2. The schematic view of the CL instrument.

were transferred to the reaction cell by the micropipette. Then 400 µl of acidic cerium(IV) was injected into the reaction cell using a micropipette and a lumbar puncture (LP) needle. The emitted light intensity at 10 s after injection of cerium(IV) solution was considered as an analytical signal.

RESULTS AND DISCUSSION

Preliminary Investigations

Effect of remifentanil was investigated in some other CL systems such as luminol-IO_4^-, direct oxidation using acidic cerium(IV) or acidic $KMnO_4$. Moreover, the effect of different dyes as a sensitizer was investigated in the $KMnO_4$-Dye CL system. The dyes used in this study were crystal violet, amido black, naphthol green, amaranth, rhodamine 6G, safranin, orange G, fluorescein, and chromotrope 2R. The results show that remifentanil has the highest CL intensity and S/B ratio in the acidic cerium(IV)-$Ru(phen)_3^{2+}$CL system. The CL intensity of remifentanil and corresponding background intensity are listed in Table 1.

Optimization of Chemical Variables

Different concentrations of the cerium(IV) solution was studied in the range of 1.0×10^{-4}-5.0×10^{-2} M to optimize

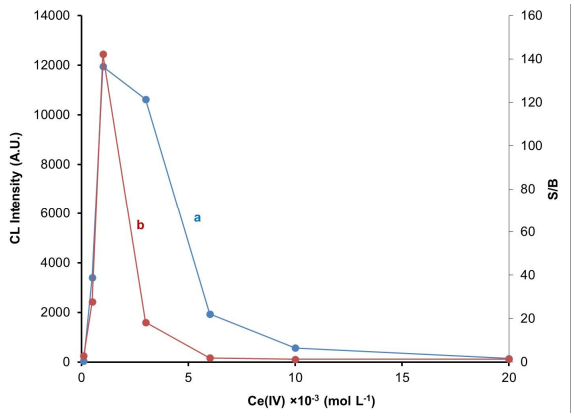

Fig. 3. Optimization of cerium(IV) concentration. a) CL of remifentanil (S) at different concentrations of cerium(IV) b) S/B ratio. Remifentanil 145.85 µg ml^{-1}, $Ru(phen)_3^{2+}$: 1.0×10^{-3} M, H_2SO_4: 0.1 M.

Table 1. Effect of Remifentanil in Different CL Systems

CL System[a]	Background intensity (B)	CL Intensity (S)	S/B
Ce/H_2SO_4	0	5	N/A
Ce/H_2SO_4-$Ru(phen)_3^{2+}$	14	6664	476.00
$KMnO_4/H_2SO_4$	19	7	0.37
$KMnO_4/H_2SO_4$-Crystal violet	15	19	1.27
$KMnO_4/H_2SO_4$-Amido black	0	6	N/A
$KMnO_4/H_2SO_4$-Naphtol green	4	3	0.75
$KMnO_4/H_2SO_4$-Amaranth	68	49	0.72
$KMnO_4/H_2SO_4$-Rhodamine 6G	214	152	0.71
$KMnO_4/H_2SO_4$-Safranin	34	31	0.91
$KMnO_4/H_2SO_4$-Orange G	33	36	1.09
$KMnO_4/H_2SO_4$-Fluorescein	40	51	1.28
$KMnO_4/H_2SO_4$-Chromotrope 2R	54	49	0.91
Luminol/Na_2CO_3	5541	8551	1.54

[a]Cerium(IV): 1.0×10^{-3} M , H_2SO_4: 0.1 M, $Ru(phen)_3^{2+}$: 1.0×10^{-3}, $KMNO_4$: 1.0×10^{-3} M, Dyes: 1.0×10^{-3} M, Luminol: 1.0×10^{-4} M, IO_4^-: 1.0×10^{-4} M, Remifentanil: 300 µg ml^{-1}.

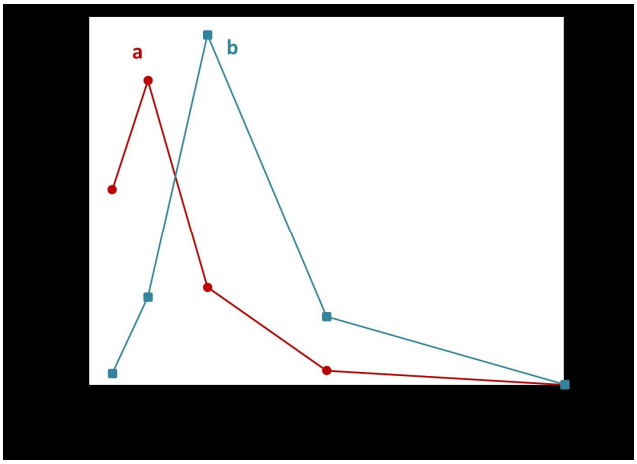

Fig. 4. Sulfuric acid concentration optimization diagram. A) CL response of remifentanil (S) at different concentrations of H_2SO_4 b) S/B ratio. Remifentanil 145.85 µg ml^{-1}, cerium(IV): 1.0×10^{-3} M, $Ru(phen)_3^{2+}$: 1.0×10^{-3} M.

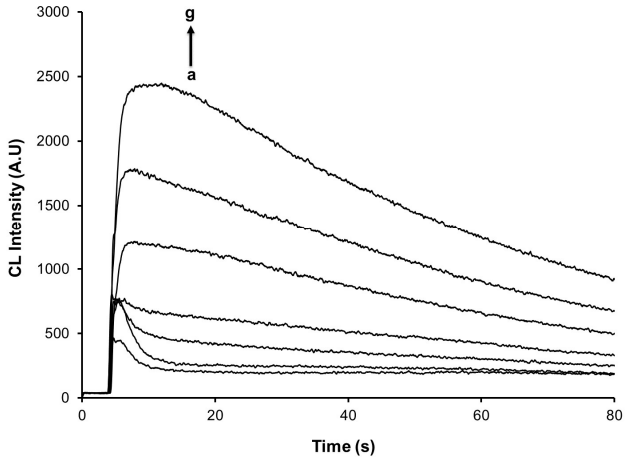

Fig. 5. Typical CL time profiles of remifentanil. a) blank, b) 1.75, c) 18.23, d) 36.46, e) 72.92, f) 109.39 and g) 182.32 µg ml^{-1}.

the effect of cerium(IV) concentration on the CL intensity of remifentanil. A concentration of 3.0×10^{-3} M cerium(IV) related to the highest ratio of S/B was considered as optimal concentration.

The concentration of sulfuric acid affects the oxidizing power of cerium(IV) and thus affects the CL intensity. To this end, it is necessary to optimize the sulfuric acid concentration. Therefore, concentrations of sulfuric acid in the range of 0.02-0.80 M were studied. As shown in Fig. 4, the concentration of 0.1 M sulfuric acid produced the highest S/B ratio and was considered optimal.

At low concentrations of sulfuric acid and cerium(IV), the oxidizing power of the solution is not enough to oxidize both $Ru(phen)_3^{2+}$ and analyte. Therefore, the CL intensity increases with the increasing concentration of sulfuric acid and cerium(IV). When the concentration of these two variables is higher than their optimum value, the analyte radical cation produced in the reaction with cerium(IV) is likely to be re-oxidized by the excess oxidant and lose its reducing power (which is necessary for reducing the $Ru(phen)_3^{3+}$ complex and emanating light). Therefore, the intensity of the light decreases.

Analytical Figures of Merit

Figure 5 shows the effect of different concentrations of the drug on the CL intensity. The maximum intensity is observed approximately 1.5 seconds after starting the CL reaction, and after 40-90 seconds, the amount of CL intensity returns to the baseline. The shape of the CL time profiles is related to the reducing power of analyte or kinetic of CL reaction. Analytes with high reducing power produce sharp and intense CL peaks, but those with low power usually produce a broad and weak peak. This characteristic of different analytes (time-resolved CL) could be used to reduce the effect of some blank interferences in plasma samples [28] or to simultaneous quantification of compounds [29,30].

The linear dynamic range was 1.75-145.85 ($I_{CL} = 13.96C_{remifentanil} + 65.66$), in which I_{CL} is CL intensity and $C_{remifentanil}$ is the concentration of remifentanil (µg ml^{-1}). Limit of detection (LOD) was 1.41 µg ml^{-1} using the equation LOD = $3S_b/m$. In this equation, S_b is the standard deviation in 10 consecutive measurements of the blank sample, and m is the slope of the calibration curve.

The method's precision was provided by the per cent of relative standard deviation (%RSD). The %RSD for four repeated determinations of 109.39 µg ml^{-1} was 2.3%.

In Table 2, some analytical features of the proposed method are compared with other reported methods. All previously proposed methods for the determination of remifentanil are based on inherently complex and expensive

Table 2. Some Analytical Characteristics of the Proposed Method in Comparison with other Methods for the Determination of Remifentanil

Method	LDR (ng ml^{-1})	LOD (ng ml^{-1})	%RSD	Sample	Ref.
HPLC	2.5-250	NR	≥15	Blood	[16]
HPLC	10-60	NR	3.4-10.7	Blood	[15]
LC-MS	0.05-50.0	0.02	4.4-6.3	Plasma	[10]
GC	0.2-100	NR	3.5-12	Blood	[19]
LC-MS/MS	0.5-48.0	0.18	3.2-5.1	Plasma	[12]
GC-HRMS-SIM	0.1-250	NR	3.5-6.3	Blood	[18]
SPE-UHPLC-MS/MS	1-20	0.2	2.51-3.48	Blood	[11]
SPE-HPLC	7.89-1500	NR	2-5	Plasma	[17]
UHPLC-MS/MS	0.25-50	NR	>10	Plasma	[13]
LC-MS	0.1-50	NR	2.7-10	Blood	[9]
CL	1750-145850	1410	2.3	Injections	Present work

HPLC: High-Performance Liquid Chromatography, MS: Mass Spectrometry, GC-HRMS-SIM: Gas Chromatography-High Resolution Mass Spectrometry-Selective Ion Monitoring, SPE-UHPLC: Solid Phase Extraction-Ultra High-Performance Liquid Chromatography. NR: Not reported.

chromatographic separations. Each of these methods has its advantages and disadvantages. There are some disadvantages, for example, using an expensive instrument, time-consuming preparation, needing an expert operator. Moreover, they are not simply amenable to be miniaturized. Although the proposed method is not more sensitive than the chromatographic methods, it is the first CL method with good sensitivity and reproducibility to determine remifentanil in pharmaceuticals. The proposed method and reagents are applicable for a wide variety of pharmaceuticals [31].

Interference Effect Study

The CL intensity of remifentanil with a concentration of 145.85 μg ml^{-1} (3.8×10^{-4} M) was measured in ten consecutive determinations in the absence of interfering species to investigate the potential interference effect of some ionic and molecular species. Then, the CL intensity of remifentanil was recorded in the presence of each interfering species with a concentration of 3.8×10^{-2} M. If the presence of an interference species caused the CL response of remifentanil to be in the range $\overline{X} \pm \frac{ts}{\sqrt{n}}$, it was not considered to be an interference. If the CL intensity was outside the range $\overline{X} \pm \frac{ts}{\sqrt{n}}$, the concentration of the species was reduced so that the CL intensity was in the range $\overline{X} \pm \frac{ts}{\sqrt{n}}$ ($\overline{X}$ and s are average CL intensity and standard deviation obtained for ten times repeated determination of 145.85 μg ml^{-1}, respectively. t is tabulated t-value at 95% confidence level for 9 degrees of freedom (t = 2.821). The results are shown in Table 3.

Application of the Method

Remifentanil ampoules were analyzed to evaluate the applicability of the proposed method. The results are shown in Table 4. The proposed method results were also compared with those obtained with a spectrophotometric method at 212 nm. Variance ratio F-test and Student's t-test were used for statistical comparison of two methods. The results showed no significant differences regard to accuracy and precision between the two methods.

CL Mechanism

The following mechanism has been proposed for the CL

Table 3. The Interference Effect of Different Species on the CL Response of Remifentanil

Substance	The molar ratio of substance/remifentanil
NH_4Cl, $NaHCO_3$, Caffeine, NaCl, Glucose, Starch, Sucrose, $ZnCl_2$	100
$MgSO_4$, CMC, Urine, $CaCl_2$, Riboflavin	50
Thiourea, Lactose, Na_2CO_3, Maleic acid, Ascorbic acid	10
Tartaric acid	1
Sodium oxalate, Trisodium citrate	0.1

Table 4. Determination of Remifentanil in Ampoules by the CL and UV-Vis Methods

Sample	Added (mg)	Found (CL, mg)[b]	Found (UV-Vis, mg)[b]	Recovery (CL, %)	t[c]	F[d]
Ampoule 1 (2 mg)[a]	0.00	2.04 ± 0.05	1.98 ± 0.04	102.0	1.62	1.56
Ampoule 2 (2 mg)[a]	0.00	1.91 ± 0.02	2.00 ± 0.06	95.5	2.46	6.25
	0.50	2.45 ± 0.12	-	108.0	-	-
	1.00	2.92 ± 0.10	-	101.0	-	-
	1.50	3.46 ± 0.17	-	103.3	-	-

[a]Based on remifentanil hydrochloride (Aburaihan Co, Iran), [b]Mean values of three replications, [c]Calculated Student t-test (theoretical value: 2.78 (P = 0.05)), [d]Calculated F, theoretical value: 19.00 (P = 0.05)).

reaction in the acidic cerium(IV)-$Ru(phen)_3^{2+}$ complex system [25,32,33]:

$$Ru(phen)_3^{2+} + Ce(IV) \rightarrow Ce(III) + Ru(phen)_3^{3+}$$

$$Ru(phen)_3^{3+} + \text{Analyte (or its oxidation products)} \rightarrow [Ru(phen)_3^{+2}]^*$$

$$Ru(phen)_3^{2+}]^* \rightarrow Ru(phen)_3^{2+} + h\upsilon\ (600\text{-}610\ nm)$$

The $Ru(phen)_3^{2+}$ complex is brown. However, when it reacts with the acidic cerium(IV) solution, the colour changes from brown to green due to $Ru(phen)_3^{3+}$ production. $Ru(phen)_3^{3+}$ could be decomposed [34] or oxidize impurities at low speed to return to $Ru(phen)_3^{2+}$. Therefore, after a few minutes, the color of the solution turns brown again. This process was checked by UV-Vis spectrophotometer; the results are shown in Fig. 6.

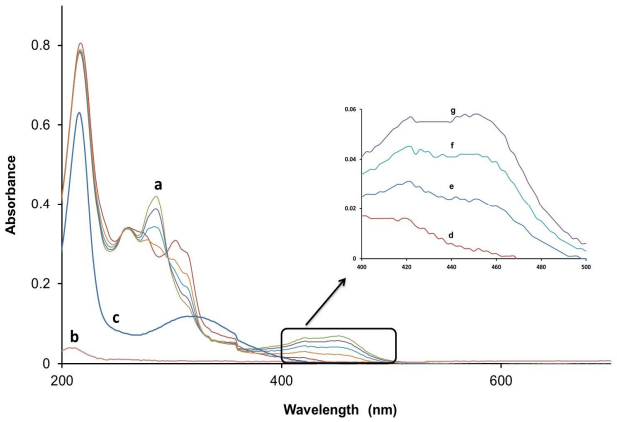

Fig. 6. UV-Vis absorption spectrum a) $Ru(phen)_3^{2+}$ 1.0×10^{-5} M, b) Remifentanil 0.72, c) Cerium(IV) 3.3×10^{-5} M in 3.3×10^{-3} M sulfuric acidand d-g) spectra of mixture of Ce(IV)-$Ru(phen)_3^{2+}$-remifentanil, 3 to 12 min after mixing and time intervals of 3 min.

According to the above UV-Vis spectra, $Ru(phen)_3^{2+}$ complex has strong absorption in the range of 400-500 nm (spectrum a). At the same time, other species (acidic solution of cerium(IV) and remifentanil) in this area have no

significant absorption. Therefore, it can be concluded that the absorption change in this area is related to the concentration of $Ru(phen)_3^{2+}$.

By adding acidic cerium(IV) solution to the $Ru(phen)_3^{2+}$ complex solution, the absorption decreases in the range of 400-500 nm (spectrum d). However, after 3 min (spectrum e), the absorption increased again due to the regeneration of $Ru(phen)_3^{2+}$ complex. The concentration of $Ru(phen)_3^{2+}$ complex increases over time (spectrum d to g) until the concentration of $Ru(phen)_3^{2+}$ complex reaches an equilibrium after 15 minutes, and its concentration changes are negligible (spectrum g).

The presence of type III amine groups in remifentanil causes the production of unstable radical cations after oxidation by cerium(IV) solution, which is capable of reducing the $Ru(phen)_3^{3+}$ complex and thus accelerating the conversion of $Ru(phen)_3^{3+}$ to $Ru(phen)_3^{2+}$ complex [35].

Overlap of the phenanthroline π orbitals in the complex of $Ru(phen)_3^{3+}$ with the radical orbitals of the analyte results in electron transfer from the analyte to the phenanthroline π* orbital. The electron is then transferred from the π*-orbital to the Ru ground-state orbital with the emission of a photon of light (about 600 nm) [34,36,37].

To prove the reducing effect of remifentanil on $Ru(phen)_3^{3+}$ complex and its effect on the conversion rate of $Ru(phen)_3^{3+}$ to $Ru(phen)_3^{2+}$ complex, the kinetics of conversion in the presence and absence of remifentanil were examined at a wavelength of 450 nm. According to Fig. 6, only the $Ru(phen)_3^{2+}$ complex has an absorbance at a wavelength of 450 nm, and other species (acidic cerium(IV) solution and remifentanil) do not have absorbance at this wavelength.

To compare the rate of conversion of the $Ru(phen)_3^{3+}$ complex to the $Ru(phen)_3^{2+}$ complex in the presence or absence of remifentanil, the reaction cell containing the $Ru(phen)_3^{2+}$ complex and the blank was placed in the cell chamber of the UV-Vis spectrophotometer. Finally, acidic cerium(IV) solution was injected into the cell's contents, and the absorption at a wavelength of 450 nm was recorded relative to time. Also, to investigate the process in the presence of the drug, the reaction cell containing the $Ru(phen)_3^{2+}$ complex and the drug was placed in the UV-Vis device, and just after injecting cerium(IV) solution, the absorbance at a wavelength of 450 nm was recorded relative to time. Figure 7 shows the effect of remifentanil on the conversion kinetics of $Ru(phen)_3^{3+}$ to $Ru(phen)_3^{2+}$.

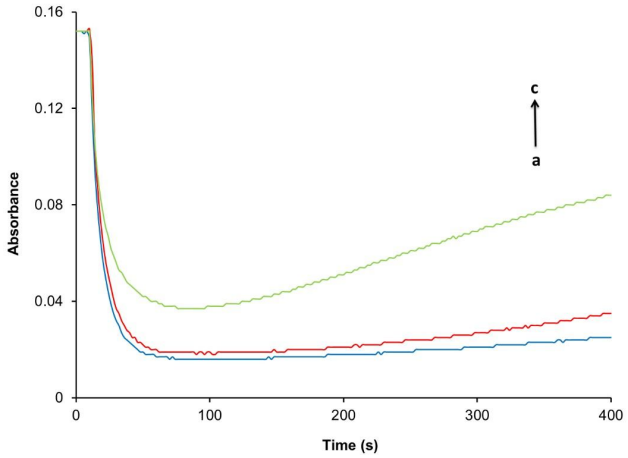

Fig. 7. Changes in concentration and absorption of $Ru(phen)_3^{2+}$ complex over time a) in the mixture of $Ru(phen)_3^{2+}$-Cerium(IV) b and c) in the mixture of $Ru(phen)_3^{2+}$-Cerium(IV)-remifentanil, $Ru(phen)_3^{2+}$: 6.6×10^{-6} M, H_2SO_4: 3.3×10^{-3} M, Creium(IV): 3.3×10^{-5} M, remifentanil: b) 72.92 μg ml^{-1}, c) 187.32 μg ml^{-1}.

As can be seen in Fig. 7, In the absence of remifentanil, the conversion process of $Ru(phen)_3^{3+}$ complex to $Ru(phen)_3^{2+}$ complex is performed at a low speed (time profile a). Moreover, The presence of remifentanil accelerates the conversion of $Ru(phen)_3^{3+}$ complex to $Ru(phen)_3^{2+}$ complex (time profile b) due to the reducing effect of remifentanil. The concentration of remifentanil directly affects the speed of the process (time profile c). These observations indicate that remifentanil can rapidly convert $Ru(phen)_3^{3+}$ complex to $Ru(phen)_3^{2+}$ complex. Therefore, the proposed mechanism was approved.

CONCLUSIONS

The proposed method is the first application of a CL reaction to determine remifentanil. All previously proposed methods for the determination of remifentanil are based on inherently complex and expensive chromatographic separations. Compared to chromatographic methods, the method is simple and low cost, with acceptable sensitivity

and precision for determining remifentanil in pharmaceutical formulations. So, the principal significance of the proposed method is the application of a simple method and low-cost instrument for many routine quality control applications.

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REFERENCES

[1] O. Grottke, P.J. Dietrich, S. Wiegels, F. Wappler, Anesth. Analg. 99 (2004) 1521.
[2] M. Knapik, P. Knapik, P. Nadziakiewicz, H. Misiołek, W. Saucha, M. Walaszczyk, A. Dyaczyńska-Herman, Med. Sci. Monit. 12 (2006) 133.
[3] M. Eidy, K. Kolahdouzan, H. Mohammadi poranvari, M. Fatemi, Anaesthesia, J. North Khorasan Univ. Med. Sci. 7 (2016) 865.
[4] P.S.A. Glass, D. Hardman, Y. Kamiyama, T.J. Quill, G. Marton, K.H. Donn, C.M. Grosse, D. Hermann, Anesth. Analg. 77 (1993) 1031.
[5] H. Bürkle, S. Dunbar, H. Van Aken, Anesth. Analg. 83 (1996) 646.
[6] B. Guignard, C. Coste, H. Costes, D.I. Sessler, C. Lebrault, W. Morris, G. Simonnet, M. Chauvin, Anesth. Analg. 95 (2002) 103.
[7] T.D. Egan, Clin. Pharmacokinet. 29 (1995) 80.
[8] M.A. El Hamd, M. Wada, R. Ikeda, S. Kawakami, N. Kuroda, K. Nakashima, Biomed. Chromatogr. 29 (2015) 325.
[9] J. Bender, J. Van Den Elshout, K. Selinger, G. Broeders, J. Dankers, C. Van Der Heiden, J. Pharm. Biomed. Anal. 21 (1999) 559.
[10] R. Said, A. Pohanka, M. Andersson, O. Beck, M. Abdel-Rehim, J. Chromatogr. B 879 (2011) 815.
[11] J. Lv, Y. Li, H. Jin, Y. Shi, Q. Xia, Y. Yang, Anal. Lett. 45 (2012) 1133.
[12] E. Bossù, A. Montinaro, R. Lecce, A. Farina, E. Suppa, G. Draisci, G. Gostoli, J. Pharm. Biomed. Anal. 42 (2006) 367.
[13] K. O'Hara, J.J. Schneider, A.L. Jones, I.M.R. Wright, J.H. Martin, P. Galettis, J. Liq. Chromatogr. Relat. Technol. 42 (2019) 521.
[14] K. Vishwanathan, J.T. Stewart, J. Liq. Chromatogr. Relat. Technol. 22 (1999) 923.
[15] K. Selinger, C. Lanzo, A. Sekut, J. Pharm. Biomed. Anal. 12 (1994) 243.
[16] S.H. Haidar, Z. Liang, K. Selinger, L.W. Hamlett, N.D. Eddington, J. Pharm. Biomed. Anal. 14 (1996) 1727.
[17] M. Kabbaj, F. Varin, J. Chromatogr. B 783 (2003) 103.
[18] C.M. Grosse, I.M. Davis, R.F. Arrendale, J. Jersey, J. Amin, J. Pharm. Biomed. Anal. 12 (1994) 195.
[19] A.R. Bjorksten, C. Chan, D.P. Crankshaw, J. Chromatogr. B 775 (2002) 97.
[20] A.C. Calokerinos, N.T. Deftereos, W.R.G. Baeyens, J. Pharm. Biomed. Anal. 13 (1995) 1063.
[21] U. Isacsson, G. Wettermark, Anal. Chim. Acta 83 (1976) 227.
[22] M. Bidlingmaier, J. Suhr, A. Ernst, Z. Wu, A. Keller, C.J. Strasburger, A. Bergmann, Clin. Chem. 55 (2009) 445.
[23] A. Garcia-Campana, W. Baeyens, L. Cuadros-Rodriguez, F. Barrero, J. Bosque-Sendra, L. Gamiz-Gracia, Curr. Org. Chem. 6 (2002) 1.
[24] M. Moazzam, M. Asghar, M. Yaqoob, S. Ali, A. Nabi, Luminescence 36 (2021) 674.
[25] A. Mokhtari, M. Ghazaeian, M. Maghsoudi, M. Keyvanfard, I. Emami, Luminescence. 30 (2015) 1094.
[26] Rezaei, A. Mokhtari, J. Braz. Chem. Soc. 22 (2011) 49.
[27] B.A. Gorman, P.S. Francis, N.W. Barnett, Analyst 131 (2006) 616.
[28] A. Mokhtaria, M. Benama, M. Keyvanfard, M. Ghazaeian, Anal. Bioanal. Chem. Res. 3 (2016) 265.
[29] A. Mokhtari, M. Keyvanfard, I. Emami, RSC Adv. 5 (2015) 29214.
[30] T. Pérez-Ruiz, C. Martínez-Lozano, V. Tomás, J. Fenoll, Anal. Chim. Acta 485 (2003) 63.
[31] R.D. Gerardi, N.W. Barnett, S.W. Lewis, Anal. Chim. Acta 378 (1999) 1.
[32] B. Rezaei, A. Mokhtari, Luminescence 23 (2008) 357.

[33] B. Rezaei, A. Mokhtari, Luminescence 24 (2009) 183.
[34] M. Hara, C.C. Waraksa, J.T. Lean, B.A. Lewis, T.E. Mallouk, J. Phys. Chem. A 104 (2000) 5275.
[35] F.A. Aly, S.A. Al-Tamimi, A.A. Alwarthan, Talanta 53 (2001) 885.
[36] W.L. Wallace, A.J. Bard, J. Phys. Chem. 83 (1979) 1350.
[37] E. Bolton, M.M. Richter, J. Chem. Educ. 78 (2001) 47.