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Flow Injection Chemiluminescence Method for Nalbuphine Hydrochloride in Pharmaceutical Formulations Using Tris(2,2′-bipyridyl)ruthenium(II) Chloride-diperiodatocuprate(III) Reaction

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A sensitive and selective method employing chemiluminescence(CL) coupled with flow injection(FI) is reported for nalbuphine hydrochloride(NAL) assay in pharmaceutical formulations. The enhancement effect of NAL on the CL reaction between tris(2,2′-bipyridyl)ruthenium(II) chloride-diperiodatocuprate(III) {$Ru[(bpy)_3]^{2+}$-Cu(III) complex} in acidic medium is used as analytical measurement. The optimal conditions of the CL reaction were sulfuric acid 1.0×10^{-3} mol/L, $Ru[(bpy)_3]^{2+}$ 7.5×10^{-5} mol/L , Cu(III)/Ag(III) complexes 4.0×10^{-4}/5.0×10^{-4} mol/L, sample loop volume of 120 μL and flow rate of 2.5 mL/min. The sensitivities of the method in terms of detection(S/N=3) and quantification(S/N=10) limits are 5×10^{-4} and 0.001 ppm(1 ppm=1 mg/L), respectively. The linear response of the instrument in the form of CL intensity with respect to NAL concentration is over the range 0.001—15.0 ppm(R^2=0.9999) with relative standard deviation from 0.8% to 3.2% and injection throughput of 120 injection/h. The applications of the method include the quantitative analysis of NAL in pharmaceutical injection samples. Variations and the average results of the proposed method are not significantly different from the results of a reported method by applying *F*- and paired student *t*-test. The most likely CL reaction mechanism is written in accordance with spectrophotometric and CL studies.

Keywords $Ru[(bpy)_3]^{2+}$; Cu(III)/Ag(III) complex; Chemiluminescence; Flow injection analysis; Nalbuphine hydrochloride; Pharmaceutical

1 Introduction

Nalbuphine hydrochloride[NAL, 17-(cyclobutylmethyl)-4,5α-epoxymorphinan-3,6α,14-triol hydrochloride] is a synthetic analgesic, which acts as an opioid agonist-antagonist and relates to the phenanthrene series. Chemically, it closely relates to naloxone(a widely used opioid antagonist) and oxymorphone(a potent opioid analgesic). The NAL is used to treat both chronic and acute pain, and its analgesic potency has been claimed as equal to morphine[1]. A few advantages of NAL over morphine include the lack of significant withdrawal symptoms, the low tolerance liability and a ceiling effect of respiratory depression[2]. However, the usage of it has also been accompanied with a few typical side effects, which encompass dizziness, vomiting, respiratory depression, abnormal blood pressure and heart rate, and most commonly sedation[3]. On human subjects, a single dose of 8 mg of nalbuphine produced subjective effects similar to morphine. Similarly, 24- and 72-mg doses of nalbuphine have resulted in barbiturate-like characteristics and weak psychotomimetic effects respectively in human subjects. When given in the usual adult dose of 7—10 mg/70 kg, nalbuphine causes respiratory depression[4].

NAL(M_w=393.90) is soluble in deionized water(35.5 mg/mL at 25 °C) and ethanol(0.8%), and insoluble in chloroform and ether. NAL has pK_a values of 8.71 and 9.96. Its chemical structure is given in Fig.1. Each milliliter of the commercially available parenteral solution contains 10 mg of NAL, sodium chloride(6.1%), sodium citrate(0.94%), citric acid anhydrous(1.26%), sodium metabisulfite(0.1%), and a mixture(9:1) of methylparaben and propylparaben(0.2%) as a preservative, and the pH is adjusted with hydrochloric acid[5].

Various analytical assays have been described to detect NAL in pharmaceutical formulations and biological fluids, which include high-performance liquid chromatography with

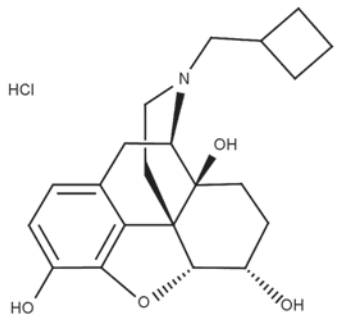

Fig.1 Chemical structure of nalbuphine hydrochloride ($C_{21}H_{27}NO_4$·HCl, M_w=393.90)

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ultraviolet, electrochemical and mass spectrometry detectors[6—10], gas chromatography with electron capture, flame ionization and mass spectrometry detectors[11—13], capillary zone electrophoresis with ultraviolet detector[14], voltammetry[15—18], potentiometry[19], spectrofluorimetry[20—23] and spectrophotometry[23—27]. The main advantages of chromatographic methods are superior selectivity and high sensitivity, but these methods are also coupled with a number of disadvantages, such as the requirement of costly instrumentations and solvents, high expertise, lengthy procedures and unavailability in common laboratories. Narrow linear range and low sensitivity are coupled with electroanalytical methods. Table 1 compares different analytical characteristics of the proposed method with already established methods for the analyses of NAL in various samples.

Chemiluminescence(CL) is a well-established analytical technique, which is the emission of electromagnetic radiations over spectrum regions including visible and near infra-red during a chemical reaction. The emitter is always an intermediate excited product. CL is an attractive analytical technique due to its simpler instrumentation, higher sensitivity and wider linear ranges, which allows the quantification of analytes in small volumes of solution[28,29]. The CL reagent namely tris(2,2′-bipyridyl)ruthenium (II) complex{$[Ru(bpy)_3]^{2+}$} gives an orange light emission centred at 610 nm and the emitter has been documented as the electronically excited $[Ru(bpy)_3]^{2+*}$. This excited chemical species can be regenerated due to an electron transfer by a reducing agent. The $[Ru(bpy)_3]^{2+}$ is the stable form of the CL reagent in contrast to $[Ru(bpy)_3]^{3+}$, which is the reactive form and can be generated from its reduced form by various means. They include the oxidation either electrically on the surface of an electrode at +1.3 V or chemically by using oxidizing agents with cerium(IV)/permanganate in acidic medium or lead dioxide. During the $[Ru(bpy)_3]^{2+}$ CL reactions, the intensity of emitted radiations is in direct proportion to the concentration of the reducing agent acting as an analyte[30—32]. Various CL reactions coupled with flow-based methodologies have been thoroughly used for the analyses of many analytes in different fields of science including beverages, food, biological, clinical, pharmaceutical and environmental science[33—38]. Different FI-CL procedures with Ag(III), Cu(III), Ni(IV) and $AuCl_4^-$ as the oxidant have been investigated for biological fluids, food and drugs analysis, and their analytical characteristics have been reviewed in tabulated form[39]. Khan *et al.*[40] reported an FI-Cl method for the assay of NAL in pharmaceuticals based on its enhancement effect on the Ag(III) complex-rhodamine B CL

Table 1 Comparison of analytical characteristics of the proposed FI-CL method with already established methods for NAL analysis*

Method	Sample matrix	LOD/ppm	LOQ /ppm	Linear range/ppm	R^2	Ref.
Spec	Pharmaceutical & human urine	1.02	3.40	4.0—80	0.9999	[24]
Spec method-I	Pharmaceuticals	0.217	0.723	1.0—4.5	0.9995	[25]
Spec method-II		0.137	0.456	1.0—6.0	0.9997	
Spec	Pharmaceuticals	0.287	0.869	1.0—20	0.9997	[26]
Spec	Pharmaceuticals	0.0678	0.226	2.0—20	0.9991	[27]
Spec	Ampoules and biological samples	0.317	1.057	1.6—12.8	0.9999	[23]
Spec-Flu	Pharmaceuticals and biological	0.04	0.11	0.5—7.0	0.9999	[20]
Spec-Flu	Pharmaceuticals and serum	0.0037	0.011	0.02—0.74	0.995	[21]
Spec-Flu	Raw material and pharmaceuticals	0.175	0.529	1.0—12	0.9997	[22]
Spec-Flu	Ampoules and biological samples	0.014	0.047	2.4—8.4	0.9997	[23]
Potentiometry	Pharmaceuticals	0.3939	NR	0.3939—3939	0.9986	[19]
Voltammetry	Pharmaceuticals	1.898×10^{-4}	NR	3.5×10^{-3}—0.03	0.993	[15]
Voltammetry	Pharmaceuticals and biological	3.54×10^{-3}	NR	0.0196—508	0.9982	[16]
Voltammetry	Biological fluids	0.0275	NR	0.0787—196.95	0.9903	[17]
Voltammetry	Biological fluids	0.013	0.044	0.05—1.25	0.997	[18]
CZE–UV	Bulk drugs, pharmaceutical & biological fluids	0.3	5.0	5.0—200	0.9997	[14]
GC-FID/MS	Biological fluid	0.05	0.1	0.1—10	0.995	[12]
GC-MS	Human hair	NR	0.18	0.18—40	0.9958	[13]
HPLC-UV	Injections	0.1	0.5	0.5—20	0.99990	[6]
HPLC-ECD	Blood & brain microdiasylate	NR	0.025	0.025—10	0.978	[7]
HPLC-UV	Pharmaceuticals	0.243	0.737	1.0—15	0.9997	[8]
UPLC-MS/MS	Human plasma	NR	5.0×10^{-5}	5.0×10^{-5}—0.020	0.9960	[9]
LC-MS/MS	Human plasma	NR	5.0×10^{-4}	5.0×10^{-4}—0.5	0.995	[10]
FI-CL	Pharmaceuticals	0.001	0.003	0.005—5	0.9999	[40]
FI-CL	Pharmaceuticals	0.0005	0.001	0.001—15.0	0.9999	This method

* GC-FID/MS, gas chromatography-flame ionization detector/mass spectrometry; CZE-UV, capillary zone electrophoresis-ultraviolet; Spec, spectrophotometry; Spec-Flu, spectrofluorimetry; LOQ, limit of quantification; R^2, correlation coefficient; LOD, limit of detection; NR, not reported; ppm, parts per million(1 ppm=1 mg/L); ECD, electrochemical detector; LC, liquid chromatography; HPLC, high performance liquid chromatography; FI-CL, flow injection-chemiluminescence.

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reaction in aqueous sulfuric acid medium with injection throughput of 150 injection/h and recovery obtained over the range from 96.08% to 106.06%.

In this work, a sensitive and fast FI-CL method for the assay of low concentration levels of NAL in pharmaceutical formulations is established. The proposed method is based on the oxidation of $[Ru(bpy)_3]^{2+}$ with Cu(III) complex enhanced by NAL analyte. Analytical criteria, such as linearity, sensitivity, precision, accuracy and recovery of the method are reported. The possible CL reaction mechanism is also discussed in brief.

2 Experimental

2.1 Reagents and Solutions

All the chemicals were of analytical reagent grade and used without further purification. Deionized water(0.067 μS/cm) was purified by ELGA Purelab Option, High Wycombe, Bucks, and used throughout the work. Potassium persulfate($K_2S_2O_8$), potassium hydroxide(KOH), cupric sulphate($CuSO_4·5H_2O$), potassium periodate(KIO_4), sulfuric acid(H_2SO_4), potassium permanganate($KMnO_4$), cerium(IV) sulfate[$Ce(SO_4)_2$], potassium bromate($KBrO_3$) and potassium ferricyanide{$K_3[Fe(CN)_6]$} were purchased from BDH Chemicals Ltd.(Poole, UK) and Merck(Darmstadt, Germany). $[Ru(bpy)_3]^{2+}$(98%) was obtained from ACROS Organics(Geel, Belgium). The pure nalbuphine HCl(NAL) was obtained from Nexus Pharma(Pvt.) Ltd.(Karachi, Pakistan) as a gift. Wares(plastic and glass) to be employed in experimental work for the preparation of stock as well as running standard solution and for other purposes were thoroughly precleaned with analytical grade surfactant, rinsed vigorously with distilled water, stored for a week in HCl solution(10%) bath, and again rinsed with distilled water followed by storage in plastic bags to save them from dust particles and other contamination. Before usage, they were again rinsed with distilled water.

H_2SO_4 commercially available 18 mol/L concentrated solution was diluted with deionized water to arrange its stock solution(5.0 mol/L). This stock solution was further diluted in the same manner for the running standard solution preparation. The stock solutions(1.0×10^{-3} mol/L) of $KMnO_4$, $KBrO_3$ and $K_3[Fe(CN)_6]$ were prepared by dissolving the required amount of each compound in deionized water, while cerium(IV) sulfate was prepared in H_2SO_4(1.0×10^{-3} mol/L) solution and the working solutions were prepared by diluting the stock solutions with deionized water and H_2SO_4, respectively. The stock solution(1.0×10^{-3} mol/L) of $[Ru(bpy)_3]^{2+}$ was prepared by dissolving 0.064 g of compound in an aqueous H_2SO_4 solution(1.0×10^{-3} mol/L) and the working solutions were prepared by diluting the stock solution with H_2SO_4(1.0×10^{-3} mol/L).

For interference studies, stock solutions of metals(1000 ppm) were prepared in deionized water. For this purpose, either their nitrate salts or commercially available atomic absorption stock solution(obtained from Merck, Darmstadt, Germany) were used. The required quantities or volume were dissolved or diluted for the preparation of stock solutions of Zn^{2+}, Cd^{2+}, Fe^{2+}, Fe^{3+}, Co^{2+}, Mg^{2+}, Ca^{2+}, Cr^{3+} and Mn^{2+}. Similarly, the 1000 ppm stock solutions of SO_4^{2-}, HCO_3^-, CO_3^{2-}, Cl^- and NO_3^- were arranged from their salts(BDH Chemicals Ltd., Poole, UK) in deionized water. To assess the interference effect of possible excipient in the pharmaceutical formulations, 100 ppm stock solutions in deionized water of various organic compounds including glucose, sodium benzoate, lactose, sorbitan mono-palmitate(not soluble in H_2O), glycerine, polyethylene glycol, sodium acetate and magnesium stearate(Merck, Darmstadt, Germany) were prepared. The working standards solutions(0.001, 0.01, 0.1 and 1.0 ppm) in deionized water of these chemical species were prepared by diluting their stocks.

The diperiodatocuprate(III){$K_5[Cu(HIO_6)_2]$, Cu(III) complex} was synthesized according to the method reported previously[41]. A 0.01 mol/L stock solution of this compound was prepared by mixing 0.125 g of $CuSO_4·5H_2O$, 0.23 g of KIO_4, 0.14 g of $Na_2S_2O_8$, and 0.8 g of KOH and dissolved in 30 mL of deionized water. The solution was heated to boiling with constant stirring for about 20 min on a hot plate. The boiling mixture turned intensely red and the boiling was continued for another 20 min for the completion of the reaction. The mixture was then cooled and diluted to 50 mL with deionized water. The stock solution obtained was stored and refrigerated at 4 °C and was found to be stable for about 5 months, and Cu(III) complex solutions were freshly prepared when needed. The Cu(III) complex was characterized by its UV-Vis spectrum, which exhibited two absorption maxima at 263 and 415 nm. The Cu(III) complex solutions were freshly prepared by dissolving an appropriate quantity of the compound in KOH(1.0×10^{-3} mol/L) solution before use. The concentration was then estimated by monitoring the absorbance at 415 nm using a double beam UV-Vis spectrophotometer(Shimadzu, Model UV-1700, Japan).

The Ag(III) complex was synthesized according to the suggested method[42]. The UV-Vis spectrum was used to characterize the complex, which exhibits two absorption peaks at 360 and 253 nm. The concentration of the prepared Ag(III) complex solution was determined by the absorbance at 360 nm. While, the Ni(IV) complex was synthesized according to a previously described procedure[43], and the concentration was determined spectrophotometrically at 410 nm[44]. Working solutions were freshly prepared by diluting standard stock solutions with KOH(1.0×10^{-3} mol/L) solution. All solutions

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were refrigerated at 4 °C.

2.2 Pharmaceutical Formulations Analyses

Various pharmaceutical ampoules containing NAL(10 mg/mL) were analysed. These ampoules were collected from the local market only for research purposes and their brand names are as Exnal[Indus Pharma(Pvt) Ltd., Karachi], Nabin[Global Pharmaceuticals(Pvt) Ltd., Islamabad], Analin[Mediicaids, Pakistan(Pvt) Ltd.] and Kinz[Sami's Specs Pharmaceuticals (Pvt) Ltd., Karachi]. The contents from one ampoule(10 mg/mL) of each brand were carefully poured into 10 mL amber colored bottles followed dilution up to 10 mL using distilled water to make the NAL concentration 1000 ppm. From these NAL ampoules stock solutions, series of aliquots(0.005, 0.025, 0.050, 0.075, 0.100 and 0.125 mL) were diluted up to 50 mL with deionized water in 50 mL volumetric flasks to make working standards of 0.1, 0.5, 1.0 1.5, 2.0 and 2.5 ppm. These standards were analysed both by the proposed FI-CL method and a reported spectrophotometric method. Using the regression equations obtained from calibration curves for both methods and dilution factors, final NAL concentrations in these samples were calculated for the validation. Furthermore, recovery experiments were also performed to check the recoveries(%) of the proposed FI-CL method.

2.3 Spectrophotometric Method

For validating the results of the proposed FI-CL method for the quantitative analysis of NAL, a reported spectrophotometric method[27] was selected. The following procedure was exhibited for NAL determination by spectrophotometric method. A series of aliquot portions that are 0.0, 0.2, 0.5, 1.0, 1.5 and 2.0 mL was taken from 100 ppm NAL stock solution into 10 mL volumetric flasks to constitute range of 0.0, 2.0, 5.0, 10.0, 15.0 and 20.0 ppm standards in 10 mL, respectively. To these aliquots was added 1.0 mol/L NaOH(1.0 mL) followed by the addition of 5.0×10^{-3} mol/L aqueous solution of $KMnO_4$(2.0 mL) and vigorous shaking. These mixtures were then diluted up to 10 mL with deionized water followed by keeping in a water bath at (40±2) °C for almost 20 min. The mixture containing 0.0 ppm of NAL was considered as a blank, against which the absorbances of other mixtures were measured spectrophotometrically in 1.0 cm quartz cuvettes at 605 nm using a double beam spectrophotometer(UV-1700, Shimadzu, Japan). Similarly, NALs containing ampoules were processed and analysed spectrophotometrically.

2.4 Apparatus and Procedure

A flow injection system employed is shown in Fig.2. A peristaltic pump(Ismatec Reglo, Switzerland) delivered all streams at a flow rate of 2.5 mL/min(per stream). PTFE tubing(0.8 mm i.d.) was used to connect all components in the flow system(0.8 mm i.d., Fisher Scientific, Loughborough, UK). A sample solution volume of 120 μL was injected into the water stream *via* a six-way rotary injection valve(Rheodyne 5020, Anachem, Luton, UK) and then mixed with the mixture of acidic $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in H_2SO_4 0.001 mol/L) solution and Cu(III)/Ag(III) complexes(4×10^{-4}/5.0×10^{-4} mol/L in 1.0×10^{-3} mol/L KOH) solution. The emitted CL was collected in glass spiral flow cell(i.d.=1.50 mm, diameter=18.0 mm) fixed in front of an end window with a photomultiplier tube(9798B, Electron Tubes Ltd., Ruislip, UK) attached to a power supply(Thorn EMI, MPS2000N, UK) operated at 950 V. The detector output was recorded using a chart recorder(BD40, Kipp & Zonen, The Netherlands).

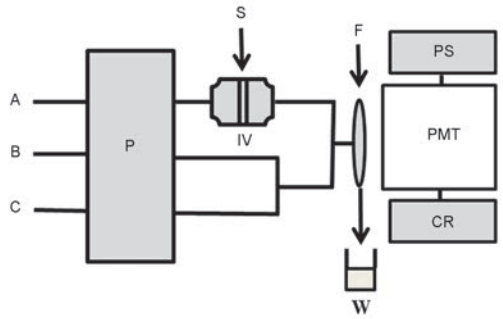

Fig.2 Schematic flow system for the assay of NAL

A, Deionized water; B, Cu(III)/Ag(III) complexes 4×10^{-4}/5.0×10^{-4} mol/L in 1.0×10^{-3} mol/L KOH solution; C, Tris(2,2′-bipyridyl)ruthenium(II) chloride hexahydrate 7.5×10^{-5} mol/L in 1.0×10^{-3} mol/L H_2SO_4 solution; P, peristaltic pump(2.5 mL/min); CR, chart recorder; PMT, photomultiplier tube detector (950 V); S, sample(120 μL); PS, power supply; W, waste; F, flow cell; IV, injection valve.

3 Results and Discussion

3.1 Optimization of the CL Reaction

In order to establish optimal experimental conditions for the lower limit of detection and suitable reproducibility, the influence of key chemical and physical variables, *e.g.*, sulfuric acid, $[Ru(bpy)_3]^{2+}$, Cu(III)/Ag(III) complexes concentrations, flow rates, sample loop volume and PMT voltage, was examined on the emission intensity of NAL standard solution(0.1 ppm). The results are reported in Fig.3 and Table 2. All the results were the mean of triplicate measurements.

The influence of $[Ru(bpy)_3]^{2+}$ concentration on the measurement of NAL was examined in the range of 0.1×10^{-5}—12.5×10^{-5} mol/L. The CL emission intensity increased up to 7.5×10^{-5} mol/L above this irreproducible and a decrease in CL intensities was detected. A $[Ru(bpy)_3]^{2+}$ concentration of 7.5×10^{-5} mol/L was then selected and utilized for all subsequent

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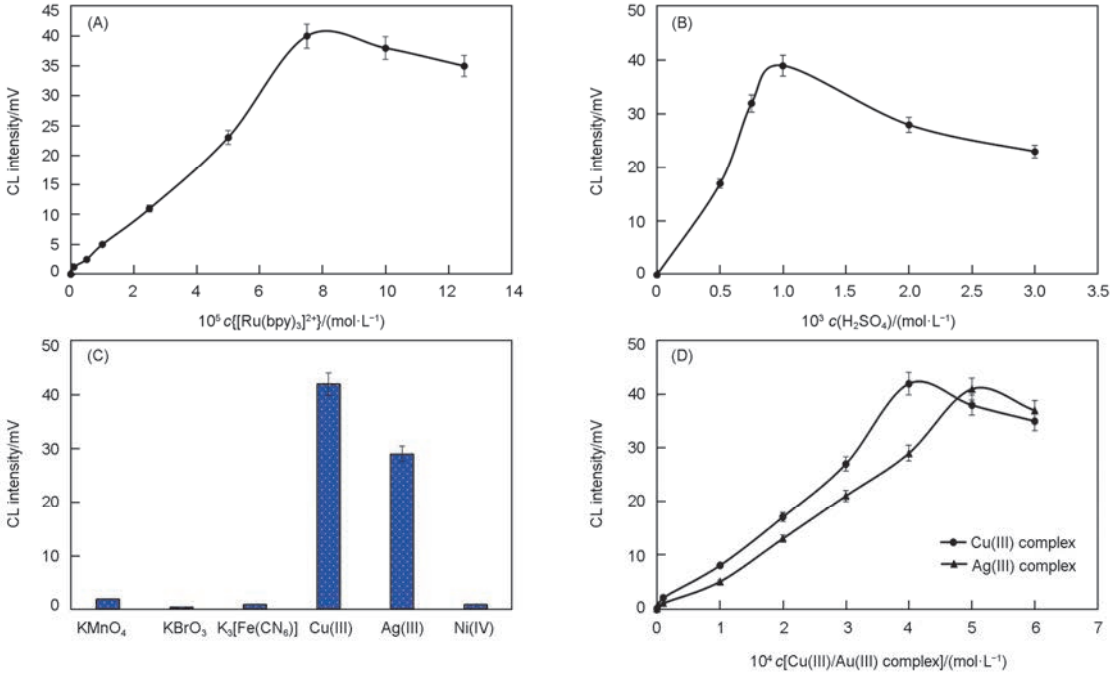

Fig.3 Optimization of concentrations of chemical reagents

(A) $[Ru(bpy)_3]^{2+}$; (B) H_2SO_4; (C) oxidants(4×10^{-4} mol/L); (D) Cu(III)/Ag(III) complexes.

Table 2 Physical parameter optimization studies for NAL determination

Method	Range studied	Optimum
Flow rate/(mL·mL^{-1})	0.5—3.5	2.5
Injected sample volume/μL	60—360	120
PMT voltage/V	800—1050	950

experiments as shown in Fig.3(A). Similarly, the influence of H_2SO_4 concentration was examined in the range of 0.5×10^{-3}—3.0×10^{-3} mol/L. The maximum CL emission intensity was detected at 1.0×10^{-3} mol/L H_2SO_4 and a further increase in a concentration resulted in a decrease in CL response as shown in Fig.3(B). Thus, H_2SO_4 concentration of 1.0×10^{-3} mol/L was selected subsequently.

The CL was emitted from the oxidation reaction of $[Ru(bpy)_3]^{2+}$ by the oxidant in the presence of NAL. Thus, the influence of various oxidants, *e.g.*, $KMnO_4$, $KBrO_3$, $K_3[Fe(CN)_6]$, Cu(III), Ag(III) and Ni(IV) complexes, was examined at the concentration level of 4.0×10^{-4} mol/L. Among these oxidants, the maximum CL response was observed when using Cu(III) complex followed by Ag(III) complex[Fig.3(C)]. Thus, the influence of Cu(III) and Ag(III) complexes concentrations was examined in the range of 0.1×10^{-4}—6.0×10^{-4} mol/L. The CL intensity was increased along with the increase in the Cu(III)/Ag(III) complexes concentrations in a lower concentration range and reached the maximum at 4.0×10^{-4} and 5.0×10^{-4} mol/L as shown in Fig.3(D), respectively. Above these concentrations, the CL intensities decreased probably due to the self-absorption of complexes at higher concentrations level. Thus, Cu(III) complex concentration of 4.0×10^{-4} mol/L was selected and used for subsequent studies. The pH of waste at optimized chemical parameters was measured as 6.62. Furthermore, NAL standard was injected into the manifold when 1.0×10^{-3} mol/L KOH and H_2SO_4 were flowing in the streams of oxidant and CL reagent, respectively, to check the effect of the neutralization reaction. As a result, no CL emission was observed, proving the stability of the CL reaction during the exothermic reaction.

The physical parameters, such as flow rate, sample loop volume and PMT voltage are important factors that influence the sensitivity of CL detection. In order to obtain satisfactory emission intensity, the influence of flow rate and injected sample volume was examined in the range 0.5—3.5 mL/min and 60—350 μL, respectively. A flow rate of 2.5 mL/min for all streams and injected sample volume of 120 μL were recommended because of the greater precision and economy in the use of sample volume and reagents. The influence of PMT voltage was examined in the range of 800—1050 V on the CL intensity of NAL. The CL intensity increased linearly with the increase in PMT voltage. However, a PMT voltage of 950 V was selected for further experiments due to high signal to noise ratio. The results are reported in Table 2.

3.2 Analytical Figures of Merit

Under the optimized conditions described above, linear calibration graphs of CL intensities *vs.* NAL concentrations

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were obtained for Cu(III) and Ag(III) complexes. The linear ranges, regression equations, limit of detections(LODs), coefficient of determinations(R^2) and RSDs are reported in Table 3. The range of RSDs(%, n=3) over the studied ranges was 1.0%—3.3%. The injection throughput was 120 injection/h. Different analytical techniques have been investigated for the assay of NAL in biological fluids and pharmaceutical formulations, and their analytical characteristics are given in Table 1 and compared with the proposed FI-CL method. This CL method has a suitable linearity range and therefore pharmaceutical samples can be analysed efficiently. Fig.4 shows the chart recorder traces over the range of 0.001—15 ppm of NAL and in the inset a calibration curve has been shown.

Table 1 reports a comparison of analytical characteristics of the proposed method with the already established reported methods for NAL determination in different samples. The proposed method is more sensitive with respect to LOD point of view than most of the reported methods. However, there are a few exceptions, which are more sensitive and accurate methods, for example, UPLC-MS/MS[9], LC-MS/MS[10] and voltammetric[15]. However, these methods are coupled with many disadvantages, such as low sample throughput, time-consuming procedures and expensive equipment. The linear dynamic range for NAL determination is quite wider compared to the proposed FI-CL method with inherent sensitivity and high sample throughput.

Table 3 Analytical characteristics for the assay of NAL(LOD and LOQ are based on S/N=3 and 10)

Species	Cu(III) complex	Ag(III) complex
Linearity/ppm	0.001—15	0.01—10
Calibration equation(x=ppm, y=mV)	y=100.23x+3.4111	y=87.41x+9.7635
Limit of detection/ppm	5.0×10^{-4}	3.0×10^{-3}
Limit of quantification/ppm	1×10^{-3}	1.0×10^{-2}
Blank signal/mV	0.20	0.5
Coefficient of determination(R^2)	0.9999	0.9998
Precision(%, RSD, n=3)	1.0—3.0	1.0—3.5
Injection frequency/h^{-1}	120	120

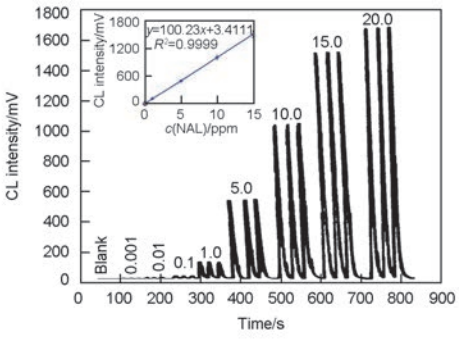

Fig.4 Calibration curve for NAL on $[Ru(bpy)_3]^{2+}$-Cu(III) under optimized chemical and physical variables(inset, a calibration graph)

3.3 Interference Study

The ampoules samples of NAL may contain some excipients. For this reason, the interference activities of cations, anions and organic compounds were checked in the presence and absence of NAL(0.1 ppm). These foreign chemical species over the concentration range of 0.001, 0.01, 0.1 and 1.0 ppm were injected into the proposed FI-CL manifold in the blank and in presence of NAL. Any chemical species, which enhances or inhibits the NAL CL signal equal to or more than 5% was listed as an interferent. Interference activities of organic compounds and different inorganic chemical species have been shown in Fig.5(A) and (B), respectively. The organic compounds, *e.g.*, sodium benzoate, glycerol, sorbitan monopalmitate, poly ethylene glycerol, magnesium stearate, crystalline cellulose, methyl cellulose and lactose, and inorganic compounds, *e.g.*, Zn^{2+}, Cd^{2+}, Fe^{2+}, Fe^{3+}, Co^{2+}, Mg^{2+}, Ca^{2+}, Cr^{3+}, Mn^{2+}, SO_4^{2-}, HCO_3^-, CO_3^{2-}, Cl^-, NO_3^- and TiO_2 did not interfer in the CL signal of NAL or in the blank. However, acetate and citrate(at 0.1 and 1.0 ppm level) slightly enhanced the CL signal of NAL(0.1 ppm). These chemical species are not commonly present in the pharmaceutical formulations. If present, they can be easily removed by using an anion exchanger resin mini online column or by precipitation. Therefore, it can be concluded that NAL can selectively be assessed in pharmaceutical formulation using the proposed FI-CL method.

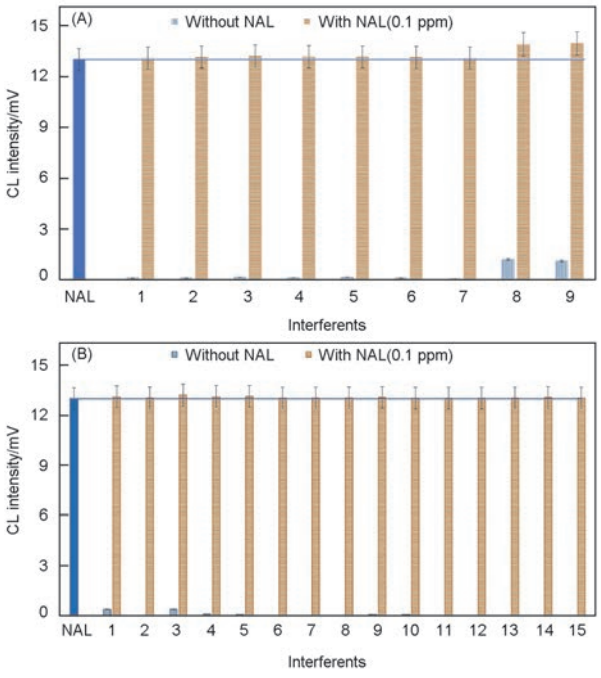

Fig.5 Effect of interferences

(A) Organic compounds: 1, Na-benzoate; 2, glycerol; 3, sorbitan monopalmitate; 4, polyethylene glycerol; 5, Mg-stearate; 6, crystalline cellulose; 7, methyl cellulose; 8, acetate; 9, citrate; (B) inorganic ions: 1, Zn^{2+}; 2, Cd^{2+}; 3, Fe^{2+}; 4, Fe^{3+}; 5, Co^{2+}; 6, Mg^{2+}; 7, Ca^{2+}; 8, Cr^{3+}; 9, Mn^{2+}; 10, SO_4^{2-}; 11, HCO_3^-; 12, CO_3^{2-}; 13, Cl^-; 14, NO_3^-; 15, TiO_2.

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3.4 Analytical Applications

To evaluate the applications of the proposed FI-CL method, NAL was monitored in the pharmaceutical injections. The recovery results are reported in Table 4. For this purpose, a series of aliquots of NAL stock solution was added to a standard solution of the ampule and analysed by the proposed method. As a result, recovery over the range of 94.2%—106.9% was obtained. In addition to the recovery experiments, the ampule pharmaceutical samples were analysed by the proposed FI-CL method and a spectrophotometric method[27] and the obtained results have been shown in Table 5. The variation and obtained results of both methods were compared by applying *F*-test and paired student *t*-test, respectively. Null hypotheses for tests of significance were retained and differences in variation and results were not due to any determinate errors but were by chance.

Table 4 Recovery of NAL from pharmaceutical ampoules with $[Ru(bpy)_3]^{2+}$-Cu(III) complex FI-CL method

Sample matrix	Spiked amount/ppm	Found amount/ppm	Recovery (%)	RSD(%, *n*=4)
Injection-I	0.00	0.054	—	2.7
	0.05	0.098	94.2	2.3
	0.10	0.157	101.9	2.1
	0.20	0.248	97.6	1.8
Injection-II	0.00	0.048	—	2.7
	0.05	0.101	103.1	2.8
	0.10	0.146	98.6	2.9
	0.20	0.252	101.6	1.9
Injection-III	0.00	0.052	—	3.2
	0.05	0.109	106.9	2.8
	0.10	0.151	99.3	2.1
	0.20	0.261	103.6	1.8

Table 5 Analysis of NAL in pharmaceutical ampoules and its comparison with a reported spectrophotometric method*

Sample matrix	Labelled amount/ ($mg \cdot mL^{-1}$)	$[Ru(bpy)_3]^{2+}$-Cu(III) complex Found amount/($mg \cdot mL^{-1}$)	
		FI-CL method	Spectrophotometric method[27]
Injection-I	10.00	9.94	9.89
Injection-II	10.00	9.83	10.53
Injection-III	10.00	10.32	10.24

* *F*-test calculated value: 1.55, *F*-distributed(p=0.05, v_1 and v_2=2)=19. Student *t*-test value: t=0.74, *t*-distributed(p=0.05, v=2)=4.30.

3.5 Kinetic Characteristics of the CL Reaction

The CL kinetic characteristics of the reaction were investigated based on the oxidation of $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in 1.0×10^{-3} mol/L H_2SO_4) by Cu(III) complex(4.0×10^{-4} mol/L in 1.0×10^{-3} mol/L KOH) and enhanced by NAL(0.25 ppm in deionized water) by utilizing the batch procedure. A typical CL intensity *vs*. time response curve was utilized to explain the CL system. As shown in Fig.6, it was observed that the reaction

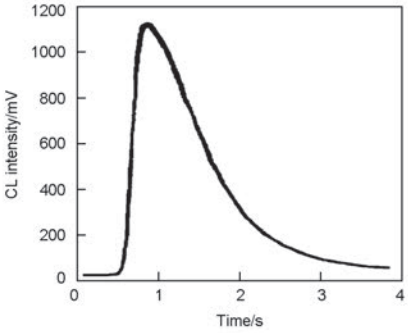

Fig.6 Kinetic characteristics of $[Ru(bpy)_3]^{2+}$-Cu(III)-NAL

Conditions: 0.5 mL of $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in 1.0×10^{-3} mol/L H_2SO_4), 0.5 mL of Cu(III) complex(4.0×10^{-4} mol/L in 1.0×10^{-3} mol/L KOH) and 0.5 mL of NAL(0.25 ppm in deionized water); PMT voltage, 950 mV; chart recorder speed, 1.0 mm/s.

was very rapid, from reagent mixing to maximum CL signal required 1.0 s for $[Ru(bpy)_3]^{2+}$-Cu(III) complex-NAL reaction and it took 4.0 s for the signal to return to the baseline. The results of the kinetic experiment prove that a sensitive and fast FI-CL method can be established for NAL estimation in pharmaceutical ampoules.

3.6 Possible CL Mechanism

For the elucidation and confirmation of the most probable CL reaction, UV-Vis spectrophotometric, spectrofluorometric and CL studies were performed.

Fig.7 and Fig.8 show spectrophotometric studies for CL reactions of Cu(III) complex-$[Ru(bpy)_3]^{2+}$-NAL and Ag(III) complex-$[Ru(bpy)_3]^{2+}$-NAL, respectively. Fig.7(A) shows two spectra, in which spectrum *a* was obtained when 1.5 mL of $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in 1.0×10^{-3} mol/L H_2SO_4) solution followed by the addition of 1.5 mL of distilled water was scanned from 200 nm to 650 nm. Maximum absorption was observed with continuums in UV and visible portions of the electromagnetic spectrum with wavelength maximum of 285 and 453 nm, respectively. Similarly, spectrum *b* was achieved when Cu(III) complex(4.0×10^{-4} mol/L in 1.0×10^{-3} mol/L KOH) was scanned. The wavelength maximum for Cu(III) complex was observed at 415 nm. In Fig.7(B), the spectrum *a* was achieved when the mixture of 1.5 mL of $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in 1.0×10^{-3} mol/L H_2SO_4) solution and 1.5 mL of Cu(III) complex(4.0×10^{-4} mol/L in 1.0×10^{-3} mol/L KOH) was scanned. The wavelength maxima both for Ru(II) and Cu(III) complexes were disappeared, showing the redox reaction, in which the former one acted as a reducing agent and the later one as an oxidizing agent. The main product of this reaction could be Ru(III). The spectrum *b* of Fig.7(B) was obtained when the aforementioned mixture was added to 100 μL of NAL(1000 ppm) constituting about 33 ppm per 3-mL. In this spectrum, the Ru(II) complex peak reappeared showing

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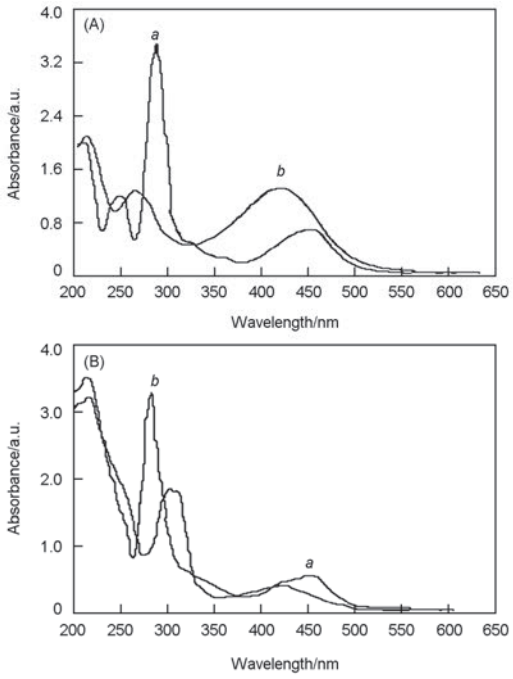

Fig.7 UV-Vis spectrophotometric studies of $[Ru(bpy)_3]^{2+}$-Cu(III) complex-NAL CL reaction

(A) Spectrum *a*, 1.5 mL of $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in H_2SO_4) solution and 1.5 mL of distilled water; spectrum *b*, Cu(III) complex(4.0×10^{-4} mol/L in KOH); (B) spectrum *a*, mixture of 1.5 mL of $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in H_2SO_4) solution and 1.5 mL of Cu(III) complex(4.0×10^{-4} mol/L in KOH); spectrum *b*, mixture of 1.5 mL of $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in H_2SO_4) solution and 1.5 mL of Cu(III) complex(4.0×10^{-4} mol/L in KOH). NAL, 33 ppm; H_2SO_4, 1.0×10^{-3} mol/L; KOH, 1.0×10^{-3} mol/L.

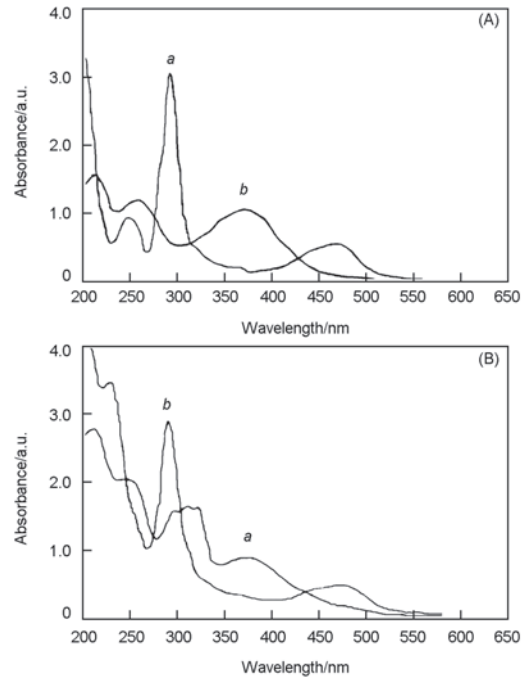

Fig.8 UV-Vis spectrophotometric studies of $[Ru(bpy)_3]^{2+}$-Ag(III) complex-NAL CL reaction

(A) Spectrum *a*, 1.5 mL of $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in H_2SO_4) solution and 1.5 mL of distilled water; spectrum *b*, Ag(III) complex(5.0×10^{-4} mol/L in KOH); (B) spectrum *a*, mixture of 1.5 mL of $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in H_2SO_4) solution and 1.5 mL of Ag(III) complex(5.0×10^{-4} mol/L in KOH); spectrum *b*, mixture of 1.5 mL of $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in H_2SO_4) solution and 1.5 mL of Ag(III) complex(5.0×10^{-4} mol/L in KOH). NAL, 33 ppm; H_2SO_4, 1.0×10^{-3} mol/L; KOH, 1×10^{-3} mol/L.

the redox reaction between NAL and Ru(III) complex, in which the former one acted as a reducing agent and the latter one as an oxidizing agent. Similarly, UV-Vis spectrophotometric studies were also performed for $[Ru(bpy)_3]^{2+}$-Ag(III) complex-NAL CL reaction as shown in Fig.8(A) and (B). Fig.8(A) shows two spectra, in which spectrum *a* was obtained for 1.5 mL of $[Ru(bpy)_3]^{2+}$ as in Fig.7, while spectrum *b* was obtained when Ag(III) complex (5.0×10^{-4} mol/L in 1.0×10^{-3} mol/L KOH) was scanned. The wavelength maximum for Ag(III) complex was observed at 258 and 353 nm. Fig.8(B) shows the similar results as shown in Fig.7(B) and the only difference was the use of Ag(III) complex as an oxidant instead of Cu(III) complex.

Fluorometric studies were performed employing a spectrofluorometer(RF-1501, Shimadzo, Japan) to confirm the emitter in CL reactions of Cu(III) complex-$[Ru(bpy)_3]^{2+}$-NAL [Fig.9(A)] and Ag(III) complex-$[Ru(bpy)_3]^{2+}$-NAL[Fig.9(B)]. In both figures, spectrum *a* was obtained for $[Ru(bpy)_3]^{2+}$ when its acidic solution was excited at 285 nm and thus 604 nm was observed as the emission wavelength maximum. The spectrum *a* in both cases was diminished almost to baseline, resulting in spectrum *b* when oxidants solutions were added to a cuvette containing $[Ru(bpy)_3]^{2+}$, suggesting its oxidation. Almost similar emission spectrum(spectrum *c*) as of $[Ru(bpy)_3]^{2+}$ was

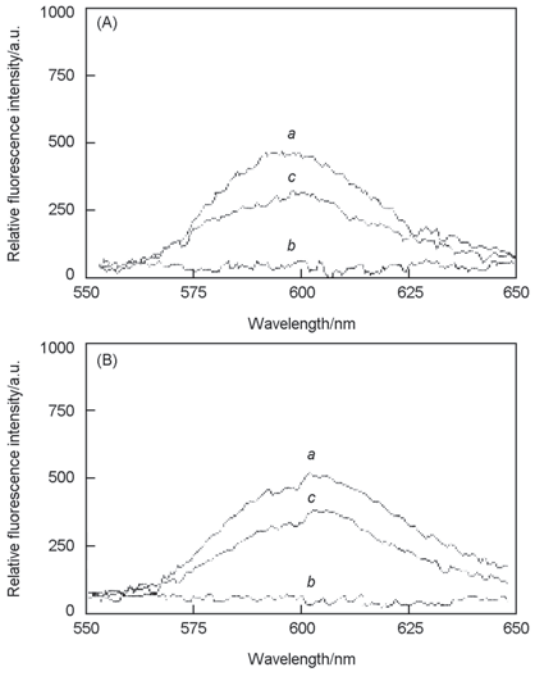

Fig.9 Spectrofluorometric studies

(A) Cu(III) complex-$[Ru(bpy)_3]^{2+}$-NAL: Curve *a*, 1.5 mL of $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in H_2SO_4) solution and 1.5 mL of distilled water; curve *b*, mixture of 1.5 mL of $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in H_2SO_4) and 1.5 mL of Cu(III) complex(4.0×10^{-4} mol/L in KOH); curve *c*, mixture of 1.5 mL of $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in H_2SO_4) solution and 1.5 mL of Cu(III) complex(4.0×10^{-4} mol/L in KOH); (B) Ag(III) complex-$[Ru(bpy)_3]^{2+}$-NAL: curve *a*, 1.5 mL of $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in H_2SO_4) solution and 1.5 mL of distilled water; curve *b*, mixture of 1.5 mL of $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in H_2SO_4) and 1.5 mL of Ag(III) complex(5.0×10^{-4} mol/L in KOH); curve *c*, mixture of 1.5 mL of $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in H_2SO_4) solution and 1.5 mL of Ag(III) complex(5.0×10^{-4} mol/L in KOH). NAL, 33 ppm; λ_{ex}=285 nm, λ_{em}=604 nm; H_2SO_4, 1×10^{-3} mol/L; KOH, 1×10^{-3} mol/L.

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observed when the solutions containing $[Ru(bpy)_3]^{3+}$ were added to NAL, suggesting its reduction.

Diperiodatocuprate(III){$K_5[Cu(HIO_6)_2]$, Cu(III) complex} is a weak oxidizing agent in alkaline medium with the reduction potential of 0.42 V(*vs*. SCE)[45]. The Cu(III) complex is the stable oxidized product of Cu^{2+} metal chelated by chelating with polydentate ligands(IO_4^-). The Cu(III) complex is a versatile one-electron oxidant for the oxidation of different organic compounds in basic medium and its use as an analytical reagent is now well recognized[41]. The formation of $[Cu(H_3IO_6)_2(OH)_2]^{3-}$ was the reactive species of water-soluble Cu(III) complex in basic medium. Like Ag(III) complex, it has been used with luminol and confirmed that the excited state of 3-aminophthalate is an emitter in the CL reaction with a maximum emission at 425 nm[46]. A similar CL mechanism with luminol-Ag(III) complex reaction has been reported based on the enhancing effect[47—53].

The CL reaction among $[Ru(bpy)_3]^{2+}$, Cu(III) complex and NAL can be written in three steps. In the first step(Step I), the $[Ru(bpy)_3]^{2+}$ is oxidized by the active form of Cu(III) complex, producing $[Ru(bpy)_3]^{3+}$. In the second step(Step II), the $[Ru(bpy)_3]^{3+}$ is reduced by NAL, producing $[Ru(bpy)_3]^{2+}$ in electronically excited state{$[Ru(bpy)_3]^{2+*}$}. This excited chemical species acts as an emitter and emitting electromagnetic radiations centered at 620 nm in the third step(Step III)[30]. The three-step CL reaction can be written as follows:

Step I:

$$[Ru(bpy)_3]^{2+}+\text{Cu(III) complex}\longrightarrow[Ru(bpy)_3]^{3+}+\text{Cu(II)(oxidation)}$$

Step II:

$$[Ru(bpy)_3]^{3+}+\text{NAL}\longrightarrow[Ru(bpy)_3^{2+}]^{*}\text{(reduction)}$$

Step III:

$$[Ru(bpy)_3^{2+}]^{*}\longrightarrow Ru(bpy)_3^{2+}+\text{Light(CL emission at 620 nm)}$$

Based on the strong enhancing effect of NAL on $[Ru(bpy)_3]^{2+}$-Cu(III) complex CL reaction, a simple and sensitive procedure was devised for the assay of NAL in pharmaceutical formulations. The optimum CL intensity was observed in the presence of Cu(III) complex at 620 nm and a much higher CL intensity in the presence of NAL, indicating that Ru(II)* was the luminophore. The Cu(III) complex is used as an oxidizing agent to generate $[Ru(bpy)_3]^{3+}$, while NAL is used as a reducing agent for enhancing the CL intensity.

Fig.10 presents the transient peaks for $[Ru(bpy)_3]^{2+}$- Cu(III) complex-NAL CL reaction in a flow mode. Curve *a* was observed when distilled water was propelled in three streams and $[Ru(bpy)_3]^{2+}$ solution was injected. As a result, no emission of CL light was detected by PMT, which suggested that Ru(II) complex did not give any CL emission in the absence of Cu(III) complex and NAL. Curve *b* was obtained when $[Ru(bpy)_3]^{2+}$ in H_2SO_4 acidic medium was propelled on its place as shown in the optimum manifold and the Cu(III) complex solution was injected into the manifold. This curve shows the background of CL emission in the absence of NAL. Similarly, curve *c* was achieved when $[Ru(bpy)_3]^{2+}$ solution in H_2SO_4 acidic medium and Cu(III) complex solution in KOH basic medium were propelled in their respective streams and NAL standard solution was injected. As a result, an enhanced CL signal was appeared, which proved that a sensitive CL method in a flow mode could be established for the analysis of NAL. The results of this experiment can also prove that a redox reaction occurs between Ru(II) and Cu(III) complexes at a specific pH, producing Ru(III) and Cu(II). Furthermore, Ru(III) complex is reduced by NAL which is a reducing agent, producing Ru(II)* complex as a CL emitter.

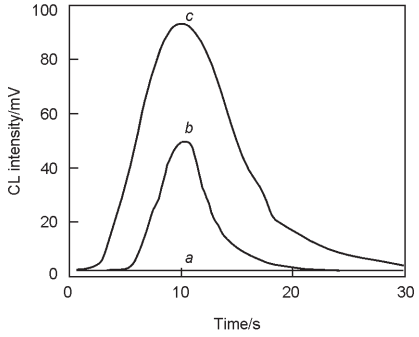

Fig.10 CL emission transient peaks for the reaction between $[Ru(bpy)_3]^{2+}$-Cu(III) complex-NAL in an aqueous sulfuric acid medium and a flow mode

Curve *a*, $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in H_2SO_4); curve *b*, $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in H_2SO_4) and Cu(III) complex(4.0×10^{-4} mol/L in KOH); curve *c*, $[Ru(bpy)_3]^{2+}$(7.5×10^{-5} mol/L in H_2SO_4) and Cu(III) complex(4.0×10^{-4} mol/L in KOH). NAL, 0.9 ppm in deionized water; H_2SO_4, 1×10^{-3} mol/L; KOH, 1×10^{-3} mol/L.

4 Conclusions

In this work, a novel CL emission system was established using $[Ru(bpy)_3]^{2+}$-Cu(III) complex reaction for the assay of NAL in an aqueous H_2SO_4 medium. The proposed procedure offers several advantages over other procedures, since it is faster and uses simpler instrumentation, high sensitivity, good linearity and precision as well as a high sample throughput up to 120 injections per hour. The method was successfully applied for the detection of NAL in pharmaceutical injections with satisfactory results. The CL reaction mechanism was also described.

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Conflicts of Interest

The authors declare no conflicts of interest.

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