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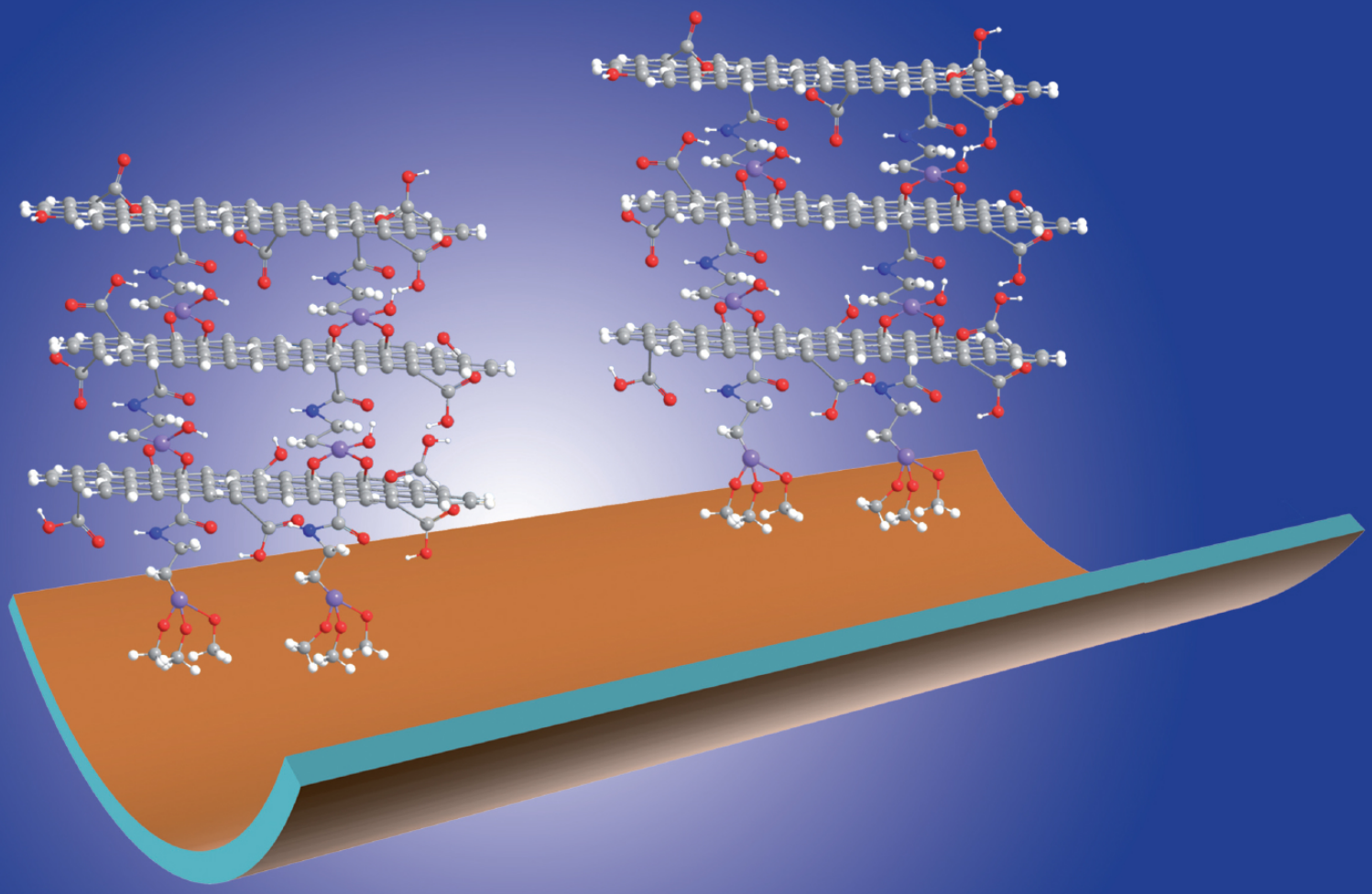

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Research Article

Capillary electrophoresis with electrochemiluminescence detection for the simultaneous determination of cisatracurium besylate and its degradation products in pharmaceutical preparations

Capillary electrophoresis with electrochemiluminescence detection for the simultaneous analysis of cisatracurium besylate and its degradation products (laudanosine, quaternary monoacrylate) in pharmaceutical preparation was developed and fully validated. The significant parameters that influence capillary electrophoresis separation and electrochemiluminescence detection were optimized. The total analysis time of the analytes was 15 min. The linearities of the method were 0.1∼40.0 μg/mL for cisatracurium besylate and 0.04 ∼8.00 μg/mL for laudanosine, with correlation coefficients (r) of 0.999 and 0.998, respectively. The detection limits (S/N = 3) were 83.0 ng/mL for cisatracurium besylate and 32.0 ng/mL for laudanosine. The intraday relative standard deviations of the analytes were <3.0%, and the interday relative standard deviations were <8.0%. The developed method was cost-effective, sensitive, fast, and resource-saving, which was suitable for the ingredient analysis in pharmaceutical preparation.

Keywords: Capillary electrophoresis / Cisatracurium besylate / Electrochemiluminescence / Laudanosine / Quaternary monoacrylate
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1 Introduction

Cisatracurium besylate, (1*R*,1′*R*,2*R*,2′*R*)-2,2′-[1,5-pentanediylbis-[oxy (3oxo-3,1-propanediyl)]-bis[1-[(3,4-dimethoxy phenyl) methyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinolinium] dibenzene sulfonate, is an intermediate-acting and nondepolarizing neuromuscular blocking agent widely used for intravenous administration for surgery [1, 2]. Cisatracurium besylate possesses good hemodynamic stability and is approximately threefold more potent than its parent drug, atracurium [3]. In addition, research showed that early administration of cisatracurium besylate for patients with acute respiratory distress syndrome could improve the survival [4, 5] and increase the time off the ventilator without increasing muscle weakness and cardiovascular side effects [6]. Weindlmayr-Goettel et al. [7] reported that Hofmann elimination inactivated cisatracurium besylate at physiological pH and temperature resulting in the formation of degradation products (laudanosine, quaternary monoacrylate). Cisatracurium besylate, under refrigeration at 5°C, also exhibited drug losses at a rate of ca. 5% per year. However, the rate of drug loss was up to ca 60% per year at room temperature [6]. The manufacturer recommended that cisatracurium besylate was refrigerated at 2–8°C to preserve potency. So, it became essential to test the effective amount in pharmaceutical preparation of cisatracurium besylate.

So far, several researches on simultaneous determination of cisatracurium besylate and its degradations in pharmaceutical preparation have been reported using HPLC with the following types of detection: charged aerosol detection [8], UV [9, 10], and MS [11]. Blazewicz et al. [8] developed an HPLC–charged aerosol detection method to simultaneously quantify cisatracurium and its degradants for pharmaceutical analysis. Although this method achieved a perfect separation, the sensitivity was low and it consumed lots of organic reagent. Wang et al. [11] detected cisatracurium besylate and its degradation products using positive ion detection by LC–MS with a satisfactory LOD, but it cost a lot and was not suitable for common analysis.

During the last two decades, CE has been developed as an efficient separation technique in pharmaceutical analysis alternatives to HPLC due to its high separation efficiency, low detection limit, wide linear range, short analysis time, and minimum consumption of samples and reagents [12–17]. Electrochemiluminescence (ECL) is a wonderful detection

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Abbreviations: **ACN**, acetonitrile; **ECL**, electrochemiluminescence; **IS**, internal standard; **PBS**, phosphate buffer solution; **Ru(bpy)$_3^{2+}$**, tris(2,2-bipyridine) ruthenium; **UD**, uniform design

method that converts electrical energy into radiative energy by an applied voltage. ECL analysis offers simplicity, high sensitivity, and low background noise and has become a greatest candidate available for coupling with CE [18–23]. Among the ECL systems, ruthenium complexes, particularly tris(2,2-bipyridine) ruthenium ($Ru(bpy)_3^{2+}$), is the most valuable in fundamental studies [24–26] because of its more stability and efficiency in aqueous phase [25]. CE with end-column ECL based on $Ru(bpy)_3^{2+}$, as an efficient and sensitive analytical technique, is widely applied for detection of a number of analytes such as amines, organic salts, nicotinamide adenine dinucleotide hydrogen, and glucose without derivatization [27, 28].

Cisatracurium besylate and its degradations as amines could enhance the ECL signal of $Ru(bpy)_3^{2+}$ greatly and could be detected directly by ECL detection. In the present study, we developed a CE–ECL method based on $Ru(bpy)_3^{2+}$ with sensitivity and wide linear range to simultaneously determinate cisatracurium besylate and its degradations. This method was cost-effective, fast, and resource-saving, and could be applied to the ingredient analysis in pharmaceutical preparation.

2 Materials and methods

2.1 Reagents and chemicals

Cisatracurium besylate and rocuronium (internal standard, IS) of analytical grade were supplied by Jiangsu Hengrui Medicine (Jiangsu, China). Laudanosine of analytical grade was acquired from ChromaDex Analytics (Boulder, CO, USA). Cisatracurium besylate for Injection was purchased from Dongying Pharmaceutical (Jiangsu, China). Tris(2,2′-bipyridyl) ruthenium(II) chloride hexahydrate ($Ru(bpy)_3Cl_2{\cdot}6H_2O$) was purchased from Sigma—Aldrich (Sigma, St. Louis, MO, USA). Acetonitrile (ACN) was of chromatographic grade and obtained from Tedia (Fairfield, OH, USA). Other chemicals of analytical grade were purchased from Chongqing Boyi Company of Chemical Reagent (Chongqing, China). Water was purified by a Milli-Q water purification system (Millipore, Milford, MA, USA).

2.2 Apparatus and methods

CE–ECL behaviors were performed on the MPI-B system (Xi'an Remax Electronics, Xi'an, China), consisting of a high-voltage power supply (0∼20 kV), an electrochemical potentiostat, an ECL detector, and a data processor. The ECL detection device was composed of a three-electrode system with a 500 μm diameter Pt disk working electrode, 1 mm diameter Pt wire auxiliary electrode, and an Ag/AgCl reference electrode. The detection cell was placed directly above the photo multiplier tube and the potential of photo multiplier tube was set at –850 V. Before use, the surface of Pt disk working electrode was polished with 0.05 μm alumina powder, and then ultrasonicated in water for 5 min to maintain good stability and reproducibility. The distance between the capillary and working electrode was kept at 50 mm. Before detection, the working electrode was scanned in water within a potential from –0.5 to 0.0 V (versus Ag/AgCl) for 20 cycles to eliminate the oxide layer deposited on the electrode. The property of the working electrode was steady for about one month with chemical treatment. A piece of uncoated fused-silica capillary (50 μm id × 360 μm od × 50 cm) was applied by Yongnian Optical Fiber Factory (Hebei, China). New capillary should be flushed with 1 M NaOH overnight. Before each experiment, the capillary was regenerated by flushed with 0.1 M NaOH, purified water, and BGE for 10 min, respectively. The capillary needed to be equilibrated with BGE for 3 min before the first run for the constant ECL signal of baseline. Between every sample injection, the capillary was rinsed with BGE for 1 min. The detection potential was set at 1.25 V. Phosphate buffer solution (PBS) of 350 μL (100 mM, pH 8.5) containing $Ru(bpy)_3^{2+}$ (2 mM) was added into the ECL detection cell, which was refreshed every 2 h during the experiments for maintaining the reproducibility. Samples were injected by electrokinetic injection at 16 kV for 3 s and the analytical time was 15 min.

2.3 Preparation of standard and pharmaceutical sample solutions

Standard stock solutions of cisatracurium, laudanosine, and rocuronium were prepared by ultrapure water at concentration of 1 mg/mL and stored at –20°C. The working solutions were further diluted in ultrapure water to a demanded concentration before use. As the absence of standard substance of cisatracurium besylate degradation, quaternary monoacrylate, the detection solution for screening CE parameters was prepared by heating the standard solution of cisatracurium besylate at 10 μg/mL for 30 min for decomposition, which contained cisatracurium besylate, laudanosine, and quaternary monoacrylate. The three components were confirmed by LC–MS/MS (Agilent 6400 Series Triple Quad, Agilent 6400, USA). The decomposed solution was kept at –20°C before use.

Cisatracurium besylate for Injection (5 mg each vial) was dissolved with ultrapure water at the concentration of 10 μg/mL, which was filtered through a 0.22 μm regenerated cellulose membrane and kept in 4°C before being detected.

3 Results and discussion

3.1 Screening CE parameters using uniform design

To achieve the global optimum for CE separation of cisatracurium besylate and its degradations speedily, the uniform design (UD) was applied in the optimization of CE parameters. UD is one of experimental designs that achieves uniformly scattered experimental points on a given domain,

Table 1. Factors investigated in the uniform design

The first sequential of uniform design				
Experiments	pH	C (mM)	V (kV)	ACN (% v/v)
1	3	20	14	10
2	3.5	40	20	10
3	4	60	12	5
4	4.5	10	18	5
5	5	30	10	0
6	5.5	50	16	0
The second sequential of uniform design				
Experiments	pH	C (mM)	V (kV)	ACN (% v/v)
1	2.7	16	14	12
2	2.8	20	18	11
3	2.9	24	13	10
4	3.0	14	17	9
5	3.1	18	12	8
6	3.2	22	15	7

whose aim is to select the most representative points in the experimental domain according to UD tables [29–31].

CE is a separation technique carried out in a narrow-bore capillary driven by external voltage. To weaken EOF of CE, ACN added into PBS was applied as BGE in our study. Thus, CE parameters mainly consist of four factors as listed below: (i) PBS pH value (pH), (ii) PBS concentration (C), (iii) separation voltage (V), and (iv) additive ACN % v/v. These variables have been demonstrated that they were significant to influence the CE process. Based on the preliminary experiments, the upper and lower limits for four significant variables were selected that pH of BGE was from 3 (lowest level) to 5.5 (highest level), and BGE concentration ranged from 20 mM (lowest level) to 50 mM (highest level), and separation voltage was arranged among 14 kV (lowest level) to 16 kV (highest level) and percent of additive ACN in PBS was from 0% v/v (lowest level) to 10% v/v (highest level). According to the factors and their ranges required as above, columns of U_6^4 table (Table 1) was applied to arrange experiments.

The results of first UD were showed as Fig. 1A. In experiment 6, the peak overlapped strongly. In experiments 4 and 5, peaks of cisatracurium besylate and its degradations were not separated well and the reason could be the resolution of analytes was affected by higher pH values. In experiment 3, the signal was lower and noise was relatively obvious possibly due to that higher concentration of PBS could bring out greater Joule heat, which would increase the viscosity of sample and adsorption on capillary wall. In experiment 1, there was indication that cisatracurium besylate, laudanosine, and quaternary monoacrylate could be separated around the given conditions. Therefore, the next runs were organized around the conditions of experiment 1 whose separation was better than other experiments. The range of buffer pH, buffer concentration, separation voltage and ACN percent were set at 2.7∼3.2, 16 ∼22 mM, 12∼18 kV, and 14∼24% v/v, respectively. The second sequential uniform was executed based on U_6^4 table (Table 1) in the same way, and the results were shown in Fig. 1B.

In this step, around the conditions of experiment 1 of the first one, the peak of every component in sample was presented in all experiments. Moreover, in experiments 1, 2, and 3, every component was achieved the complete separation. It was known that high voltage could shorten migration time, however, Joule heat also increased with the increasing voltage which was negative for separation and detection. For good peak profile and detection sensitivity, experiment 3 was chosen as the optimized result that PBS (24 mmol/L, pH 2.9) containing 10% v/v ACN as the BGE and 13 kV potential was applied as separation voltage.

3.2 Optimization of detection conditions

3.2.1 ECL emission mechanism

Recently, the determination of amines has become one of the most active areas of research in $Ru(bpy)_3^{2+}$ ECL system because of their intense ECL emission [32]. To better optimize the reaction conditions and electrochemical parameters, the mechanism of governing photoemission should be understood. Two kinds of possible reaction mechanisms of $Ru(bpy)_3^{2+}$ with cisatracurium besylate and its degradation products are deduced and presented in Fig. 2(I) and (II), respectively. As shown in Fig. 2(I), $Ru(bpy)_3^{2+}$ is oxidized to $Ru(bpy)_3^{3+}$ on electrode surface using a positive voltage. Meanwhile, cisatracurium besylate and quaternary monoacrylate, two quaternary ammonium compounds, lose a proton on C_α position to convert anion (B), which is oxidized to form an active radical (C). The active radical (C) is deprotonated further, immediately reacting with $Ru(bpy)_3^{3+}$ to generate excited-state $Ru(bpy)_3^{2+}$*. $Ru(bpy)_3^{2+}$* emits photons and gives out light when it decays to the ground state, $Ru(bpy)_3^{2+}$. In addition, in Fig. 2(II), the oxidation of laudanosine, as a tertiary amine, is understood to produce a short-lived radical cation (B′), whose α-carbon is then deprotonated, forming a strongly reducing intermediate (C'). This intermediate (C') transfers an electron to $Ru(bpy)_3^{3+}$, the oxidization product of $Ru(bpy)_3^{2+}$, to form $Ru(bpy)_3^{2+}$* which stores a great deal of chemical energy that converts light finally.

3.2.2 pH Values of detection buffer

Buffer pH value in detection cell is a very important parameter to affect ECL signal intensity. A pH value of PBS from 6.5 to 9.0 was observed in this experiment and the influence of the pH value on the detection sensitivity was shown in Fig. 3A. The results indicated that the ECL signal intensity increased with the buffer pH value rising from 6.5 to 8.5, however, the ECL signal intensity began to decrease as the buffer pH value

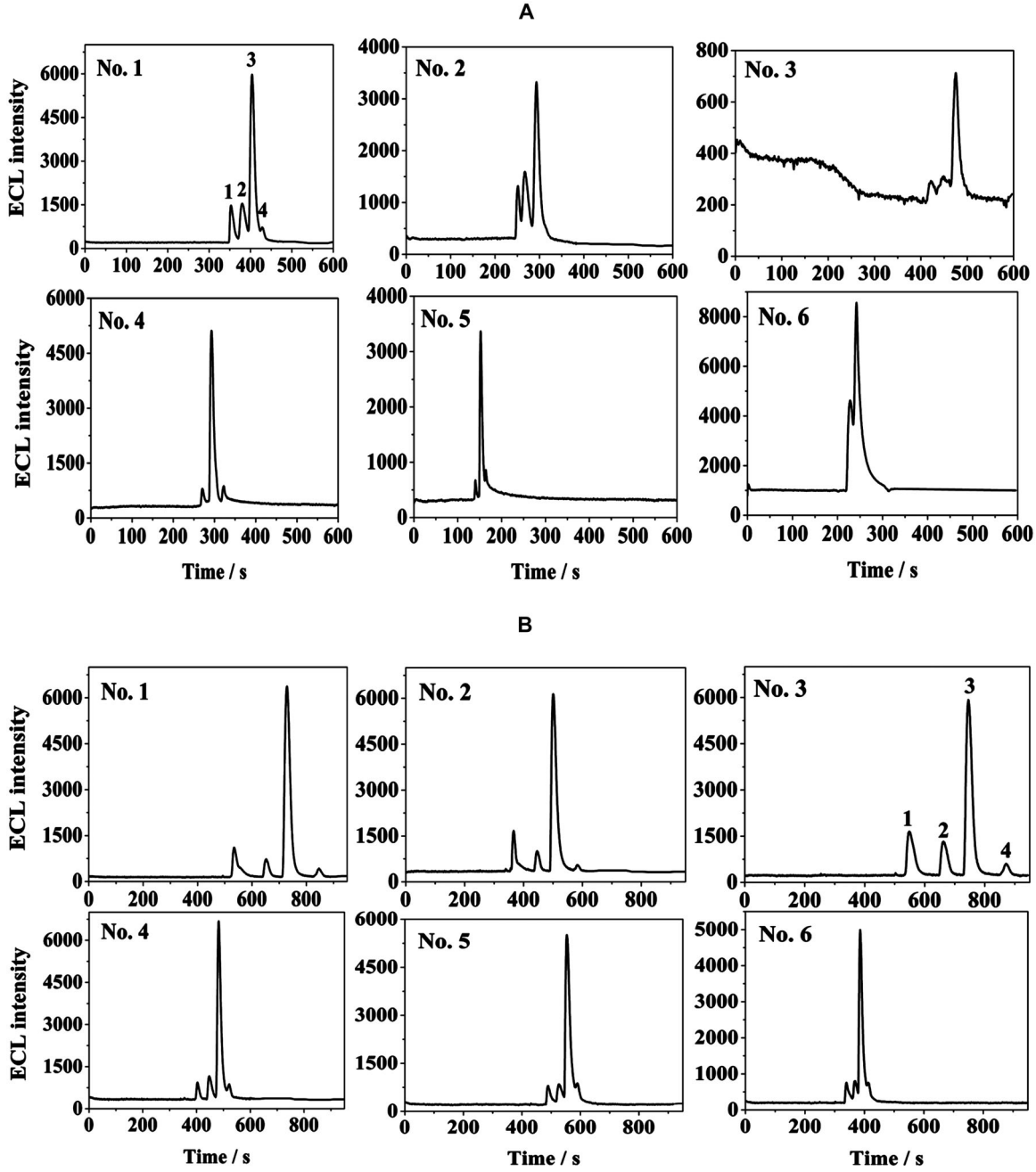

Figure 1. **(A)** The result of first uniform design; **(B)** The result of second uniform design (1. rocuronium (IS); 2. cisatracurium besylate; 3. laudanosine; 4. quaternary monoacrylate. Conditions: 10 μg/mL cisatracurium besylate standard sample with 5 μg/mL IS heated for 30 min injected into CE; The injection time was 3 s and injection voltage was 16 kV; 100 mmol/L pH 8.5 PBS containing 2.0 mmol/L $Ru(bpy)_3^{2+}$ were added in detection cell.)

continued to rise. Thus, buffer pH value of 8.5 was used for further study.

According to the proposed mechanisms, the oxidation and deprotonation of amines to form a reducing radical intermediate is the critical step in the ECL reaction. Under alkaline conditions, abundant OH^- anions facilitate the deprotonation of amines, which contribute to the high ECL emission. Note that the ECL signal intensity of laudanosine is significantly higher than that of cisatracurium besylate and rocuronium, which is probably due to the structural differences in analytes. Many studies [26, 32–34], reported that the tertiary amine group enhanced the intensity of ECL emission most among the amine structures. Knight et al. [32] reported that for tertiary amine, the formation of trigonal planar structure around nitrogen atom could increase the stability of the positive nitrogen radical formed in the ECL reaction, thus

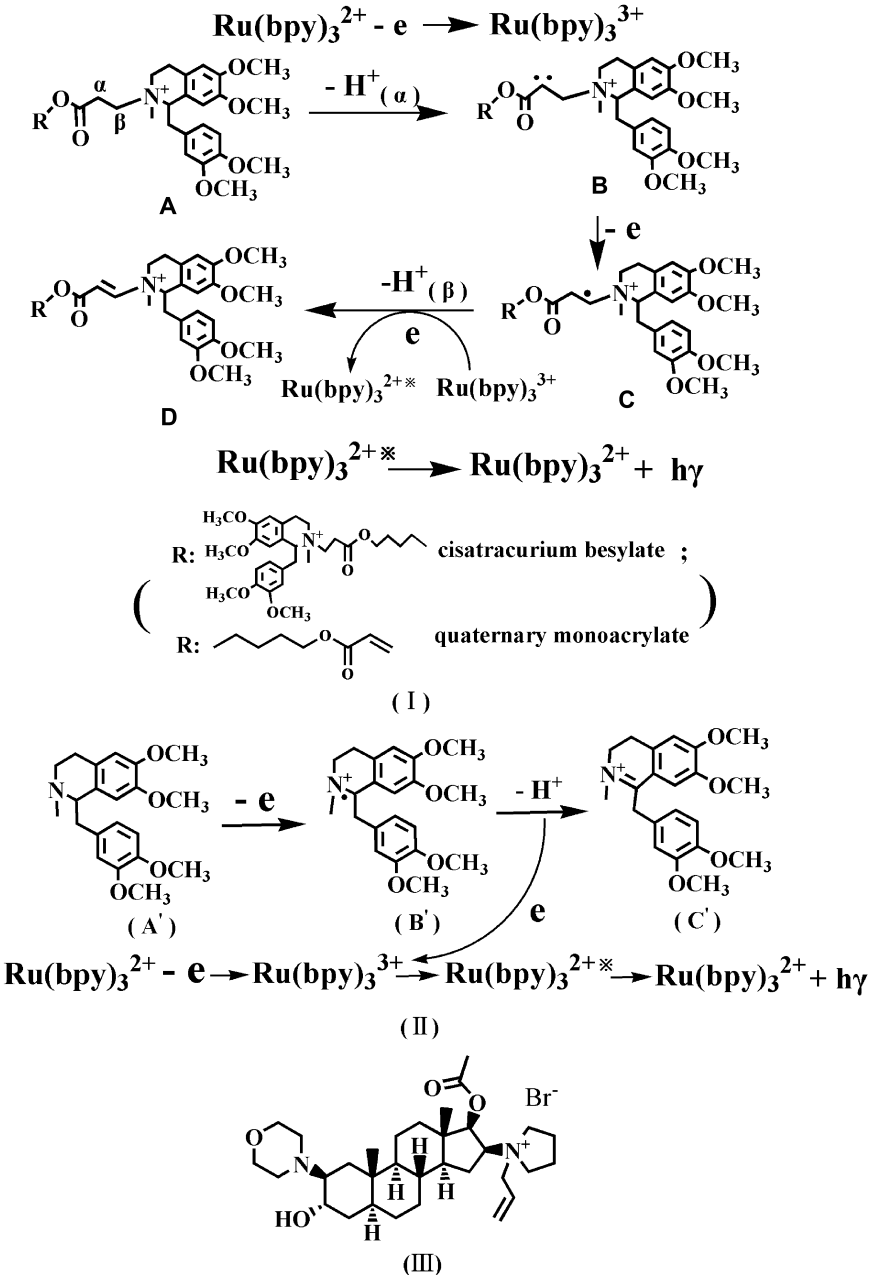

Figure 2. The mechanism of ECL reaction of cisatracurium besylate and quaternary monoacrylate (I), laudanosine (II) to give out light. The chemical structure of rocuronium (IS) (III).

enhancing the ECL intensity. The nitrogen atom of laudanosine, fixed in a six-membered ring, has a methyl group that is free to move to allow the nitrogen to adopt a more planar configuration on electro-oxidation. Hence, the formation of the positive radical is stabilized and a strong ECL response has been obtained. However, in rocuronium, the attainment of planarity is inhibited due to strong steric hindrance, so the weak ECL response is observed (Fig. 2(III))

3.2.3 Concentration of $Ru(bpy)_3^{2+}$

The concentration of $Ru(bpy)_3^{2+}$ has a large effect on the ECL intensity. Therefore, the $Ru(bpy)_3^{2+}$ concentration was investigated in the range of 0.5–3.0 mM, as shown in Fig. 3B. It was found that the ECL signal intensity increased with the elevating concentration of $Ru(bpy)_3^{2+}$ from 0.2 to 2.0 mM. When the $Ru(bpy)_3^{2+}$ concentration continued to rise, the ECL signal intensity decreased gradually. Moreover, It was known that a high concentration of $Ru(bpy)_3^{2+}$ could also lead to low S/N and poor reproducibility. Thus a 2.0 mM $Ru(bpy)_3^{2+}$ solution was chosen.

3.2.4 Selection of detection potential

The ECL reaction is voltage dependent and the oxidation of $Ru(bpy)_3^{2+}$ needs to be driven by applied potential. The

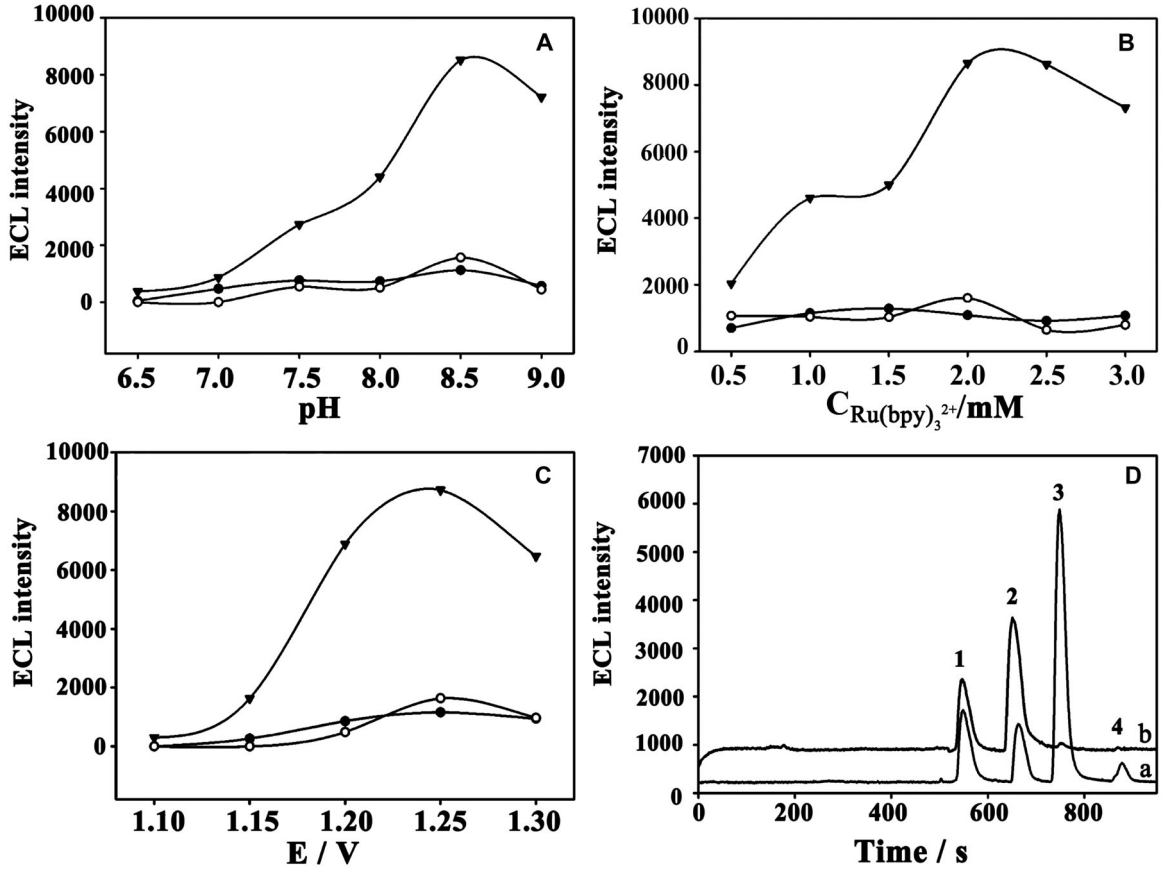

Figure 3. Effect of detection conditions on ECL intensity (A) pH value, (B) concentration of $Ru(bpy)_3^{2+}$, (C) detection potential. (○: 5 μg/mL cisatracurium besylate; ▲: 8 μg/mL laudanosine; ●: 5 μg/mL rocuronium (IS); no standard substance of quaternary monoacrylate) (D) The electropherograms of standard sample containing 10 μg/mL cisatracurium besylate and 5 μg/mL IS heated for 30 min (a), 10 μg/mL cisatracurium besylate injection sample with 5 μg/mL IS (b). (1. rocuronium (IS); 2. cisatracurium besylate; 3. laudanosine; 4. quaternary monoacrylate).

relationship between the ECL intensity and the detection potential was studied by varying the potential from 1.1 to 1.3 V. The result was shown in Fig. 3C. With increasing of detection potential, the ECL intensity increased remarkably. When the potential reached the maximum at 1.25 V, the ECL intensity signal began to decrease with the increasing detection potential. We noted that over-high potential would cause the hydrolysis of water on electrode surface and also increase background signal and the noise, consequently, the potential of 1.25 V was selected.

3.3 Method validation

3.3.1 Linearity and detection limit

A series of concentrations of cisatracurium besylate and laudanosine standard solutions were prepared by diluting stock solutions using ultrapure water, respectively, to which 5 μg/mL IS was added. Under the optimized conditions, the ECL signal intensity of those standard solutions was determined. The regression analysis was constructed by plotting the peak area ratio of cisatracurium besylate or laudanosine over IS (y) versus the concentration of standard solutions (x) revealed that the method was linear ($y = 0.0637x - 0.0018$, $r = 0.999$; $y = 0.698x + 0.0205$, $r = 0.998$ for cisatracurium besylate and laudanosine, respectively). The linearities of cisatracurium besylate and laudanosine were 0.1∼40.0 and 0.04∼8.00 μg/mL with detection limits (S/N = 3) of 83.0 and 32.0 ng/mL, respectively. Compared with earlier reports [8, 10], this developed method achieved higher sensitivity and wider linear working range.

3.3.2 Precision

The intra- and interassay repeatability for standard solutions of cisatracurium besylate and laudanosine in low, medium, and high concentrations were assessed and shown in Table 2. Intra-assay RSD ($n = 5$) was 0.9–2.3% (cisatracurium besylate) and 1.0–2.8% (laudanosine). Interassay RSD ($n = 5$) was 2.7–7.6% (cisatracurium besylate) and 5.3–5.5% (laudanosine).

Table 2. Precision and Spiked recoveries for cisatracurium besylate and laudanosine

		Precision ($n = 5$)				Spiked recoveries[a)] ($n = 3$)		
		intraday		interday		Found	Recovery	
	Concentration (μg/mL)	Mean ± SD (μg/mL)	RSD (%)	Mean ± SD (μg/mL)	RSD (%)	Mean ± SD (μg/mL)	Mean ± SD (%)	RSD (%)
Cisatracurium besylate								
Low	1.0	0.96 ± 0.00	0.9	0.89 ± 0.02	2.7	10.96 ± 0.02	96.07 ± 1.86	1.9
Medium	5.0	4.88 ± 0.10	2.1	4.57 ± 0.24	5.4	14.93 ± 0.14	98.64 ± 2.74	2.8
High	20.0	19.60 ± 0.45	2.3	17.83 ± 1.35	7.6	30.32 ± 0.73	101.58 ± 3.63	3.6
Laudanosine								
Low	0.4	0.38 ± 0.00	1.0	0.36 ± 0.02	5.4	0.39 ± 0.00	97.50 ± 1.02	1.1
Medium	2.0	1.91 ± 0.04	1.9	1.81 ± 0.10	5.5	1.89 ± 0.05	94.53 ± 2.58	2.7
High	8.0	7.86 ± 0.22	2.8	7.34 ± 0.39	5.3	8.11 ± 0.19	101.33 ± 2.34	2.3

a)The background of spiked recoveries was 10 μg/mL Cisatracurium besylate for Injection.

3.3.3 Recovery

The recoveries of analytes were assessed by spiked injection samples at low, medium and high concentrations and the data was listed in Table 2. Mean recoveries were 96.1∼101.6% for cisatracurium besylate and 94.5∼101.3% for laudanosine. The recovery RSDs of cisatracurium besylate and laudanosine were in the range from 1.94 to 3.57% and from 1.05 to 2.72%, respectively.

3.4 Detection of pharmaceutical sample

The CE–ECL method was used for the determination of the available Cisatracurium besylate for Injection (5 mg, Dongying Pharmaceutical). The result of detection achieved (90 ± 2.5)% ($n = 3$) of the labeled amount, which was in agreement with the total value as claimed by manufacturer. The typical electropherogram of active pharmaceutical ingredient of the cisatracurium besylate for injection was shown in Fig. 3D. The result indicated the feasibility of the assay for the ingredient analysis of cisatracurium besylate drug.

4 Conclusion

In this study, a CE–ECL method was developed and fully validated for the simultaneous determination of cisatracurium besylate and its degradation products in pharmaceutical preparation. CE with high separation efficiency allowed the analysis to be performed within the excellent separation of analytes. UD design realized the fast and complete optimization of CE parameters to obtain the best signal of the measurement. The developed CE–ECL method was cost-effective, sensitive, fast, and resource-saving, and suitable for the ingredient analysis of cisatracurium besylate drug.

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The authors have declared no conflict of interest.

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