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SIMULTANEOUS DETERMINATION OF ANAESTHETIC AND ANTIBOTIC IN FLUID BY ELECTOCHEMILUMINESCENCE COUPLING CAPILLARY ELECTROPHORESIS

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ABSTRACT

The coupling of electrochemiluminescence (ECL) with capillary electrophoresis (CE) was developed for the simultaneous determination of lidocaine and lomefloxacin in human urine. Under the optimized conditions: ECL detection at 1.15 V, 20 mM phosphate buffer at pH 6.7, 5 mM $Ru(bpy)_3^{2+}$ and 60 mM phosphate buffer at pH 7.6 in the detection reservoir, detection limits of 0.02 μg mL^{-1} for lidocaine and 0.06 μg mL^{-1} for lomefloxacin were obtained. Relative standard derivations of the ECL intensity and the migration time were 3.5 and 1.1% for 6 μg mL^{-1} lidocaine, 3.2% and 3.7% and 1.2% for 6 μg mL^{-1} lomefloxacin, respectively. Developed method was successfully applied to determine the amounts of lidocaine and lomefloxacin in human urine. A baseline separation for lodocaine, proline and lomefloxacin was achieved within 10 min.

KEYWORDS: Electrochemiluminescence, Capillary electrophoresis, Lidocaine, Lomefloxacin.

1. INTRODUCTION

Lidocaine(2-(diethylamino)-N-(2,6-dimethylphenyl)-acetamide) (Fig.1), an amide synthesized from cocaine, is one of the most extensively used local anesthetics and peripheral analgesic, which is effective to reduce pain.[1] Lidocaine toxicity primarily affects the cardiovascular and central nervous system and over-dosed intake may result in ventricular arrhythmia. Less than 10% of lidocaine is excreted unchanged by the urine.[1] The quantification of the lidocaine has been reported by using several methods. The Chinese

Pharmacopoeia described a titration detection method for lidocaine by perchloric acid.[2] Other methods include high performance liquid chromatography (HPLC),[3,4] spectrophotometry,[5, 6] chemiluminescence (CL)[7] and capillary electrophoresis.[1]

Lomefloxacin[1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid] (Fig.1) is one of the synthetic antibacterial fluoroquinolone agents of the third generation, which exhibits high activity against a broad spectrum of gram-negative and gram-positive bacteria. This synthetic fluoroquinolone derivative is used in treatment of infections of respiratory tract, urinary tract, joints, skin, mouth, ear, nose, throat, eye and in obstetric and gynaecological infections.[8] The widespread use of this compound and the need for clinical and pharmacological study require to establish a fast and sensitive analytical technique for detection of the drug in several biological fluids.

Over the past years, several methods for the quantification of LFLX have been reported, including HPLC-UV/fluorimetric detection,[9,10] chemiluminescence (CL),[11] Spectrophotometry,[12,13] oscillopolarography[14], differential-pulse adsorptive stripping voltammetry,[15] Fluorescence spectrometry[16] and capillary electrophoresis.[17] However, these methods requirt more sophisticated instrumentation, or are more time- consuming. Thus, it is very important to develop a simple and rapid method to detect lidocaine, proline and lomefloxacin.

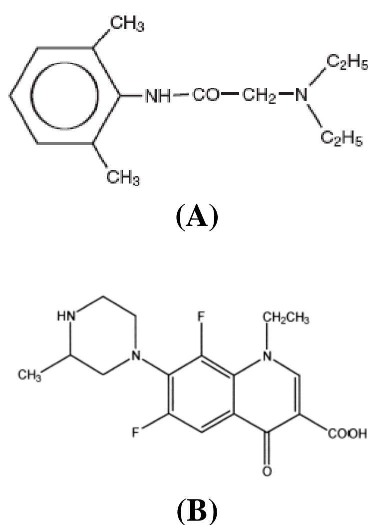

Fig. 1: Structure of lidocaine (A) and lomeflixacin (B).

Capillary electrophoresis (CE) has increasingly become an efficient separation technique. Separations with several hundred thousand theoretical plates have already been achieved even with simple capillary zone electrophoresis in its early day.[18] The high efficiency,

powerful resolution, fast separation, low instrumental cost, and low consumption of samples and reagents are the main advantage of CE over high performance liquid chromatography (HPLC). It has been widely used in analysis of amino acids,[19] anticancer drugs,[20] antibiotics,[21] veterinary drugs[22] and herbicides.[23] The most commonly used detection modes available for CE are fluorescence detection, laser-induced fluorescence detection,[24,25] UV-visible spectrophotometric detection,[26,27] mass spectrometry,[28] chemiluminescence (CL)[29] and electrochemiluminescence (ECL) detection.[30] ECL detection, in comparison with other modes, offers lower background noise, higher detection sensitivity and requires simple and inexpensive instrumentation. The luminescence compounds undergo an electron-transfer reaction at the electrode surface to form excited states that can emit light. Tris(2,2'-bipydidyl)ruthenium(II), $Ru(bpy)_3^{2+}$, has been applied for the detection of illicit drugs,[31] antibiotics[32] and some clinical medicines.[33,34]

In this paper, we used the $Ru(bpy)_3^{2+}$ based electrochemiluminescence detection as an alternative to the determination of lidocaine, proline and lemofloxacin, which were expected to be the efficient co-reactants of $Ru(bpy)_3^{2+}$ during the electrochemical reaction. Both separation and electrochemical reaction parameters were optimized in order to achieve good resolution and high sensitivity.

2. MATERIALS AND METHODS

2.1 Reagents and apparatus

Proline was obtained from Sigma, USA. Tris(2,2'-bipydidyl)ruthenium(II) chloride hexahydrate was (TBR) purchased from Aldrich Chemical Co. (Milwaukee, WI, USA). Lidocaine and lomefloxacin was obtained from Institute of Medical Biotechnology(Beijing, China). Standard stock solutions of lidocaine, lemofloxacin were prepared with double-distilled water prepared by Milli-Q ultra-high purity water system and stored at 4◦C in a refrigeratory. Working standard solutions were prepared by precise dilution of standard stock solutions with double-distilled water. Phosphate buffer both used in the detection cell and as electrophoresis running buffer was prepared by equimolar amount of disodium hydrogenphosphate and sodium dihydrogenphosphate. The appropriate pH of the buffer was adjusted with orthophosphoric acid or sodium hydroxide. Human urine was provided by healthy volunteer. All chemicals, including phosphate, sodium hydroxide were of analytical grade. The double-distilled water was prepared using Mili-Q ultra-high purity water system (XGJ-30 water purified system, Yongcheng Company in Beijing, China). Prior to CE analysis, the drug solution and buffer were filtered through a 0.22 μm membrane before use.

2.2 CE-ECL system

All experiments were carried out on a computer controlled CE–ECL system (Xi'an Remax Electronics Co. Ltd. Xi'an, China), including a high voltage power supply for electrophoretic separation and electrokinetic injection, a potential control system, a chemiluminescence detector and a data processor. A three-electrode configuration was used in the detection system consisting of a 500 µm Pt disk as a working electrode, Ag/AgCl as a reference electrode and Pt wire as a counter electrode. The end-column detection was employed by using a wall-jet configuration. Separation voltage was set at 15 kV. ECL detection reservoir used herein is the same as that reported previously.[35,29] In the reservoir, a solution of 5 mM $Ru(bpy)_3^{2+}$ and 60 mM phosphate buffer was replaced once for 4 h. Separations were performed in 35 cm long fused-silica capillaries (Yongnian Optical Fabric Factory Hebei, China) with a 25 µm i.d and 360 µm o.d. The capillary was filled with 0.1 mol L^{-1} sodium hydroxide over night. Prior to starting a series of analyses, the capillary was washed with 0.1 mol L^{-1} sodium hydroxide for 5 min, followed by double-distilled water for 5 min, and equilibrated with the running buffer for 5 min so as to maintain an active and reproducible inner surface. The voltage of photomultiplier tube for collecting the ECL signal was set at -800 V in the process of detection. Electrokinetic injected for 10 s at 10 kV. Every run was repeated at least three times under the same conditions.

2.3 Sample preparation

A 1 mL volume of urine sample was deproteinized by adding 1.0 mL 10% trichloroacetic acid (CCl3COOH) in a centrifuge tube, which was then centrifuged for 15 min at 4000 rev. min^{-1}. The centrifugate was required for urine samples. Human urine was kindly provided by healthy people collected from student volunteers in the laboratory.

3. RESULTS AND DISCUSSION

3.1. Method optimization

3.1.1. Effect of detection potential

The electrochemiluminescence reaction is voltage dependent and the oxidation of Ru $(bpy)_3^{2+}$ needs to be at least 1.0 V. We measured the ECL intensity at a variety of applied potentials and the results were illustrated in Fig. 2. The highest ECL intensity was at 1.15 V as shown in the hydrodynamic voltammograms, hence, the most sensitive detection potential for lidocaine and lomefloacin should maintain at 1.15V.

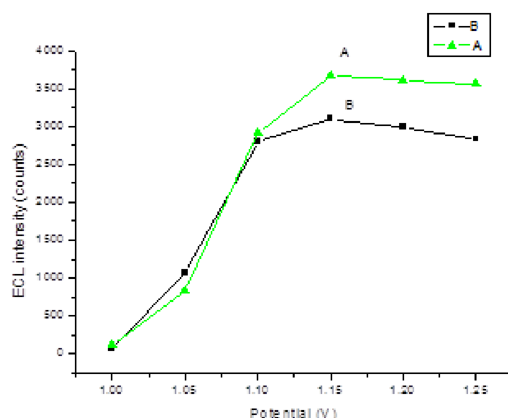

Fig. 2: Effect of detection potential on ECL intensity. ECL intensity of 60 µg mL^{-1} lidocaine (A) and 60 µg mL^{-1} lomefloxacin (B). 5mM $Ru(bpy)_3^{2+}$ and 50mM phosphate buffer in the detection reservoir; separation phosphate buffer(pH=8.0), 10mM; separation voltage, 15 kV.

3.1.2. Optimization of detection conditions

3.1.2.1 Effect of buffer pH in detection reservoir

The pH value of ECL solution is an important factor affecting the ECL intensity.[36,37] The structure of the two analytes is given in Fig. 1. The deprotonation step of analyte in ECL reaction should be the important factor to affect the ECL intensity, and therefore, the effect of the pH on ECL intensities of the three analytes was tested from pH 4.5 to 11.5 of 50 mmol L^{-1} phosphate buffer. It is clear that ECL intensity is strongly dependent on the pH of the environment. Fig. 3 showed the effect of pH value on the ECL intensity of lidocaine and lomefloxacin. From the result we can see the ECL intensity of lidocaine changed slightly, the ECL intensity of lomefloxacin increased with the pH value till an ECL intensity peak appeared at the pH value of 7.6 then keeped the intensity. At very low pH values the analytes radical cation is difficult to deprotonate to form high reducing free radical intermediate. When the pH is basic enough, the ECL intensity increases dramatically. But at high pHs the ECL intensity decreased resulted from the reduced availability of $Ru(bpy)_3^{3+}$ due to the competitive reaction with hydroxide ion which assumed high concentration levers at high pHs.[38] As the results shown above, the solution at pH 7.6 was chosen with a compromise.

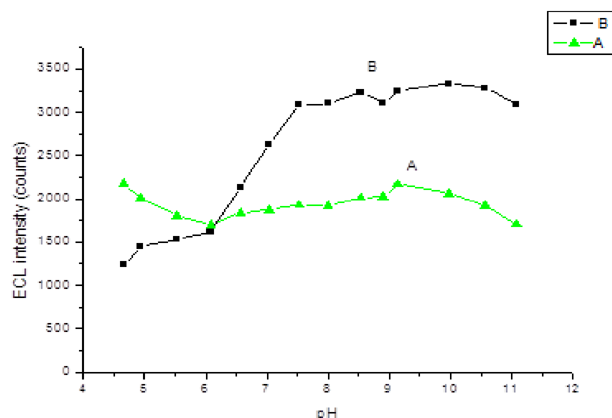

Fig. 3: Effect of pH of the phosphate buffer on ECL intensity. ECL intensity of 60 µg mL^{-1} lidocaine (A) and 60 µg mL^{-1} lomefloxacin (B). 5mM $Ru(bpy)_3^{2+}$ and 50 mM phosphate buffer in the detection reservoir; separation phosphate buffer(pH=8.0), 10 mM; separation voltage, 15 kV.

3.1.2.2. Effect of buffer concentration in detection reservoir

Another investigation of the concentration of the buffer in the detection cell was also performed. The concentration changed from 20 mM to 80 mM (pH 7.6) (Fig.4) and the highest ECL intensity of lidocaine and lomefloxacin was get at 60 mM. The ionic strength of background electrolyte is too low to transfer electrons which were produced in the electrochemical steps that resulting in the decreased ECL efficiency. As the concentration of background electrolyte is too high the quantity of $Ru(bpy)_3{}^{2+}$ ions in the vicinity of the working electrode will be reduced because other ions may replace $Ru(bpy)_3{}^{2+}$ near the electrode. The two factors reach a compromise at a concentration of 60 mM.

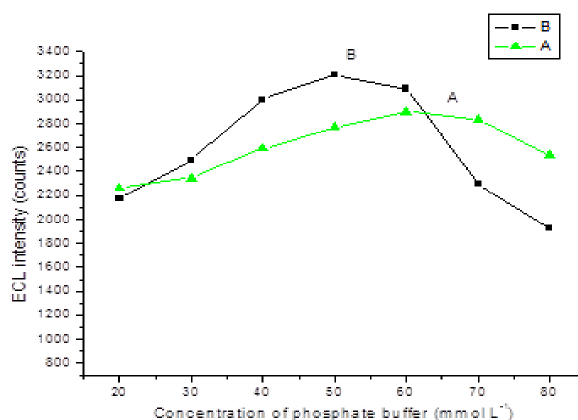

Fig. 4 The effect of concentration of the phosphate buffer on ECL intensity. ECL intensity of 60 µg mL^{-1} lidocaine (A) and 60 µg mL^{-1} lomefloxacin (B). 5mM $Ru(bpy)_3^{2+}$ nd phosphate buffer(pH=7.6) in the detection reservoir; separation phosphate buffer(pH=8.0), 10 mM; separation voltage, 15 kV.

3.1.2.3. Effect of TBR concentration in detection reservoir

One of the most important detection parameters is the optimal concentration of $Ru(bpy)_3^{2+}$.[39] A low concentration of $Ru(bpy)_3^{2+}$ leads to a low background noise. High sensitivity is obtained with increasing the concentration of $Ru(bpy)_3^{2+}$ at the same time the background noise increased and larger amount of expensive reagent ($Ru(bpy)_3Cl_2$•$6H_2O$) was consumed. Fig. 5 showed the effect of the concentration of $Ru(bpy)_3^{2+}$ on the ECL intensity of lidocaine and lomefloxacin. To get a higher S/N value and ECL efficiency and a moderate reagent consumption, 5 mM $Ru(bpy)_3^{2+}$ was used in our experiment. After an operation for 3-4 h it was needed to replenish the $Ru(bpy)_3^{2+}$ solution in order to maintain good reproducibility.

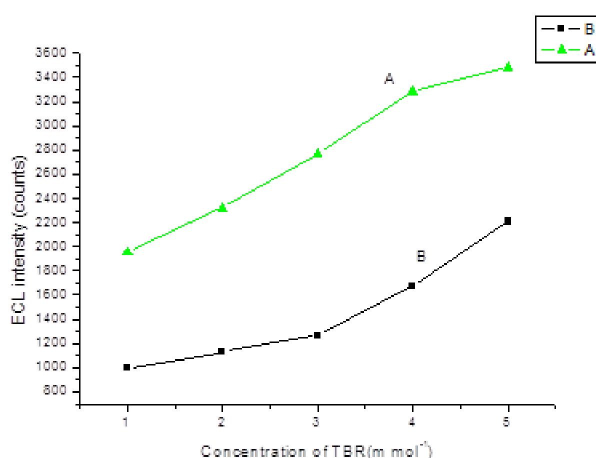

Fig. 5: The effect of concentration of TBR on ECL intensity. ECL intensity of 60 µg mL^{-1} lidocaine (A) and 60 µg mL^{-1} lomefloxacin (B). 60 mM phosphate buffer (pH=7.6) in the detection reservoir; separation phophate buffer (pH=8.0), 10 mM; separation voltage, 15 kV.

3.1.3. Optimization of separation conditions

3.1.3.1. Effect of separation buffer pH

The separation buffer pH influences not only the net charge of the analytes, but also the electro-osmotic flow inside the capillary, which, in turn, results in different migration times for analytes. Therefore, it is vital to investigate its influence on CE in order to obtain optimum separations. When the buffer pH from 5 to 11.5 was used, the peaks of lidocaine and lomefloxacin was completely separation (Rs>2) when the pH is 6.7. The resolution (Rs) between lidocaine and lomefloxacin is calculated with the following equation: $Rs = 2(t_2 - t_1)/(W_{b1} + W_{b2})$, where t_1 and t_2 are migration times of lidocaine and lomefloxacin, respectively, W_{b1} and W_{b2} are the peak widths of lidocaine and lomefloxacin measured at the

baseline. The ECL intensity of lidocaine and lomefloxacin was studied in the pH value of running buffer ranging from 5 to 11.5 too (Fig.6). Considering some major parameters such as ECL intensity and maximum separation as well as migration time, the pH value of running buffer was optimized at 6.7.

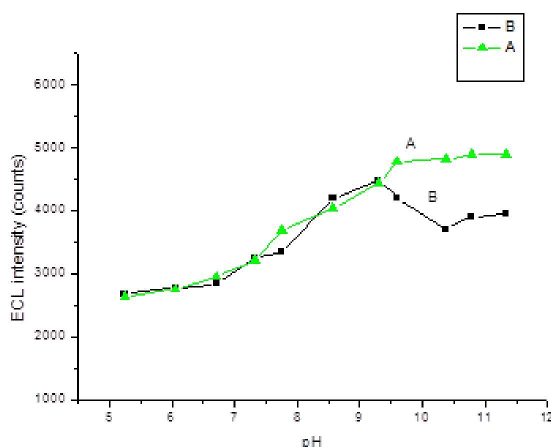

Fig. 6: The effect of pH of the phosphate buffer in capillary on ECL intensity. ECL intensity of 60 μg mL^{-1} lidocaine (A) and 60 μg mL^{-1} lomefloxacin (B). 5 mM $Ru(bpy)_3^{2+}$ and 60 mM phosphate buffer (pH=7.6) in the detection reservoir; separation phosphate buffer, 10 mM; Separation voltage, 15 kV.

3.1.3.2. Effect of separation buffer concentration

The effect of the concentration of phosphate buffer on ECL intensity and the separation of the lidocaine and lomefloxacin was tested at a pH of 6.7 in the buffer solution(Fig. 7). Over the concentration range examined (5-30 mM phosphate), the two species were baseline separated. However, the migration time of each individual species increased with the increase of the buffer concentration. But the solutions lower than 10 mM phosphate buffers give deficient buffer capacity. The concentration at 20 mM was found to be best conditions for the separation of the lidocaine and lomefloxacin in CE–ECL system. Thus, a 20 mM phosphate buffer was chosen as separation buffer in further experiment.

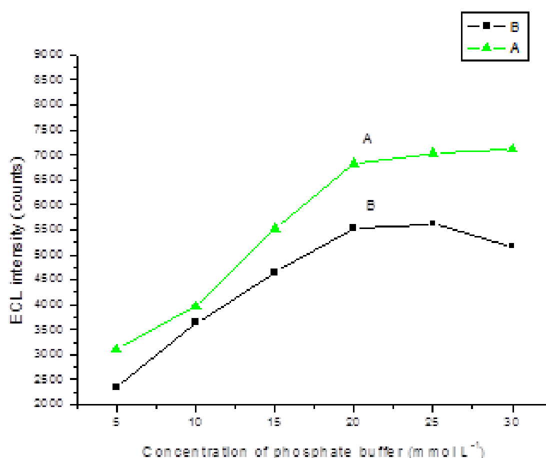

Fig. 7: The effect of concentration of the phosphate buffer in capillary on ECL intensity. ECL intensity of 60 μg mL^{-1} lidocaine (A) and 60 μg mL^{-1} lomefloxacin (B). 5 mM Ru(bpy)$_3^{2+}$ and 60 mM phosphate buffer (pH=7.6) in the detection reservoir; separation phosphate buffer(pH=6.7); separation voltage, 15 kV.

3.1.4. Linearity, detection limit and Repeatability

Under the optimized conditions: ECL detection at 1.15 V, 20 mM phosphate buffer at pH 6.7, 5 mM Ru(bpy)$_3^{2+}$ and 60 mM phosphate buffer at pH 7.6 in the detection reservoir, a standard mixture solution containing 6 μg mL^{-1} lidocaine and lomefloxacin was injected consecutively eleven times to determine the repeatability of ECL intensity based on peak height and migration time for the lidocaine and lomefloxacin. Relative standard derivations of the ECL intensity and the migration time were 3.5 and 1.1% for lidocaine, 3.7 and 1.2% for lomefloxacin, respectively. To investigate the detection linearity of lidocaine and lomefloxacin by CE–ECL, a series of standard mixture solutions containing three species were tested. The standard curves were linear between 0.1 and 100 μg mL^{-1} for lidocaine and between 0.2 and 80 μg mL^{-1} for lomefloxacin, respectively. The calibration equations and regression coefficients were: $y = 110.9x+1635.4$ and $R = 0.996$ for lidocaine, $y = 46.5x+538.6$ and $R = 0.996$ for lomefloxacin in terms of peak height response as a function of analyte concentration. Detection limit of 0.02 μg mL-1 for lidocaine and 0.06 μg mL^{-1} for lomefloxacin were obtained (S/N = 3). Compared with traditional CE method, the present method displayed good performance with sensitivity, selectivity, simplicity and rapidity.

3.2. Application to body fluid

The proposed CE-ECL method was applied to the determination of lidocaine and lomefloxacin in the human urine under the optimized conditions. The healthy volunteer was

treated simultaneously with an oral administration of 400 mg lomefloxacin tablets. The urine samples were collected at 4 h after oral administration of the drug. The urine collected before dosing was employed as a blank. All urine samples were treated as shown in Section 2 and examined with CE-ECL system. Electropherograms of standard and urine sample of lidocaine and lomefloxacin are shown in Fig.8. The results for the urine samples content and the recoveries are summarized in Table 1.

Table 1: Determination results and recovery rates of the urine samples.

Analyte	Time (h)	Content (ug mL^{-1})	Added (ug mL^{-1})	Found (ug mL^{-1})	Recovery (%)	RSD (n=5)(%)
Lidocaine	0-4	0	50	47.1	94.2	4.2
	4-8	0	50	48.3	96.6	4.4
	8-12	0	6	5.7	94.9	3.9
	12-24	0	6	5.6	93.3	4.1
Lomefloxacin	0-4	22.3	20	41.5	96.6	4.4
	4-8	21.8	20	40.9	95.5	4.9
	8-12	15.7	20	35.0	96.5	4.7
	12-24	11.5	20	30.4	94.5	4.3

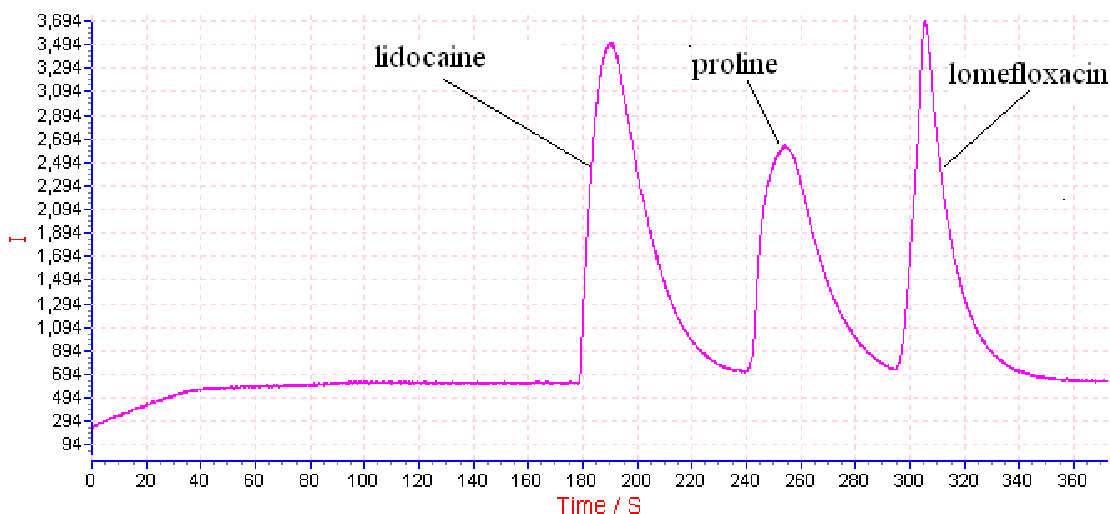

Fig. 8: Electropherograms of the solution mixed with LDC and LFLX in standard and urine sample. 5 mM $Ru(bpy)_3^{2+}$ and 60 mM phosphate buffer (pH=7.6) in the detection reservoir; separation phosphate buffer 20 mM (pH=6.7); separation voltage, 15 kV.

4. CONCUSION

A new method has been developed to determine lidocaine and lomefloxacin body fluid. Under the optimized conditions, the approach of CE-ECL with $Ru(bpy)_3^{2+}$ showed good performance in terms of selectivity, sensitivity, repeatability, short analysis time and

linearity. The validated method could be a good tool for the assay of lidocaine and lomefloxacin body fluid.

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