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Chemometrics optimization of six antihistamines separations by capillary electrophoresis with electrochemiluminescence detection

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ABSTRACT

This work expanded the knowledge of the use of chemometric experimental design in optimizing of six antihistamines separations by capillary electrophoresis with electrochemiluminescence detection. Specially, central composite design was employed for optimizing the three critical electrophoretic variables (Tris–H_3PO_4 buffer concentration, buffer pH value and separation voltage) using the chromatography resolution statistic function (CRS function) as the response variable. The optimum conditions were established from empirical model: 24.2 mM Tris–H_3PO_4 buffer (pH 2.7) with separation voltage of 15.9 kV. Applying theses conditions, the six antihistamines (carbinoxamine, chlorpheniramine, cyproheptadine, doxylamine, diphenhydramine and ephedrine) could be simultaneous separated in less than 22 min. Our results indicate that the chemometrics optimization method can greatly simplify the optimization procedure for multi-component analysis. The proposed method was also validated for linearity, repeatability and sensitivity, and was successfully applied to determine these antihistamine drugs in urine.

1. Introduction

The antihistamine drugs (seen in Fig. 1), such as carbinoxamine (CAR), chlorpheniramine (CHL), cyproheptadine (CY), diphenhydramine (DIP), doxylamine (DOX), and ephedrine (EPH) have been widely prescribed for the treatment of allergic disorders caused by histamine release [1–3]. The improper dosage of these antihistamines may cause severe sedative effects including fatigue, low blood pressure and decompensation [4]. In consideration of administration safety, a rapid and reliable analytical method is required to detect those chemicals quickly and to determine their desirable dosage.

The main methods developed for the antihistamine determination are chromatographic methods (GC, HPLC) [5–12]. However, these approaches often need complex sample pretreatment procedures and large amounts of organic solvents. On the contrary, capillary electrophoresis (CE) is advantageous for its low reagent and sample consumption, fast speed, high separation efficiency. In addition, CE can be compatible with several detection systems, such as UV detection, DAD detection, laser-induced fluorescence (LIF) and mass spectrometry (MS) detection [13–18]. However, these methods have disadvantages of being less sensitive (UV detection) or high operational cost (LIF and MS). Recently, electrochemiluminescence detection (ECL) has been proved to be a sensitive and cheap detection technique for CE [19–21]. Our previous study revealed that CE-ECL can display good sensitivity for imipramine and trimipramine [22].

Besides the sensitivity, a rapid CE optimizing process for the operating condition is highly desirable for fast determination in clinical analysis. Many factors can influence the CE performance, such as buffer composition, buffer pH value, separation voltage, injection conditions and temperature. The optimization process is very important and many efforts have been focused on the development of efficient optimization approaches. The most common approach is performed by varying one factor at a time whilst keeping the others constant, which would be rather laborious and omit interaction effects between experimental variables [23]. On the contrary, a multivariate chemometric approach allows simultaneous evaluation of all chosen factors affecting response variable and avoids complex and laborious experiments [24,25]. By using this chemometric approach, it is possible to evaluate the interaction of factors, which makes the optimization of conditions more easy and reliable. In addition, it can help to promote the statistical interpretation by producing the surface response plots and predicting the considered responses over the whole domain [25]. One of such statistical strategies is central composite design [24–26]. Central composite design is still not much used for optimizing purposes although it can greatly simplify the optimization procedure for multi-component analysis. To our knowledge, only few studies

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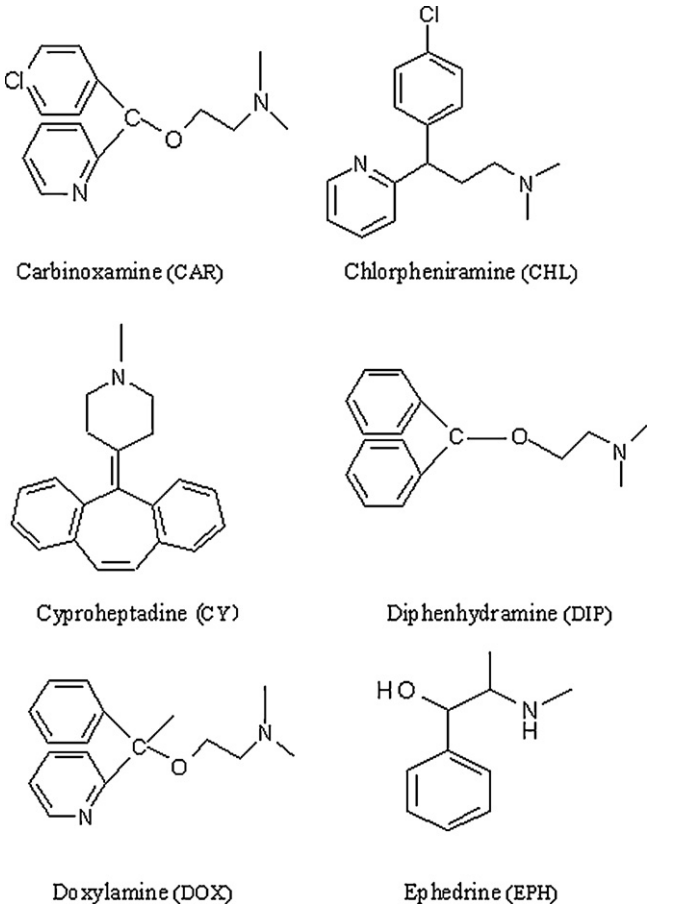

Fig. 1. Chemical structures of (a) CAR, (b) CHL, (c) CY, (d) DIP, (e) DOX and (f) EPH.

were reported on its applications in optimizing processes of CE-UV and CE-MS [13,27–35]. However, this optimization procedure has not been used in CE-ECL system yet.

The aim of this study was to develop a simple and rapid CE-ECL method for the quantitative detection of CAR, CHL, DIP, DOX, CY and EPH. For this purpose, central composite design was implemented to optimize the CE-ECL separation condition. To verify the performance of the proposed model, the predicted values were compared with the experimental results. The proposed CE-ECL method was also applied in the analysis of these drugs in urine.

2. Materials and methods

2.1. Reagents and chemicals

Tris(hydroxymethyl)aminomethane (Tris), Tris(2,2′-bipyridyl) ruthenium(II)dichloride hexahydrate ($Ru(bpy)_3Cl_2{\cdot}6H_2O$), DOX, CY, CHL and DIP were purchased from Aldrich Chemical Co. (Milwaukee, WI, USA) and used without further purification. EPH was obtained from Jilin Institute of Drug Control (Jilin, China). CAR was purchased from Fluka (Sweden). All of the reagents were of analytical grade. Double-distilled water was prepared by a Milli-Q water purification system (Millipore, Bedford, MA, USA). 10 mM sample stock solution and 0.2 mM Tris–H_3PO_4 buffer solutions were prepared with doubly distilled water. The desired sample solutions were freshly prepared by serial dilution in doubly distilled water. All standard solutions were weekly prepared and stored at 4 °C in refrigerator.

Human urine was provided by healthy volunteers. Prior to the analysis, the urine sample was diluted by 40-fold and filtered through a 0.22 μm cellulose acetate membrane.

In addition, the samples were prepared in pure water. The conductivity of the samples was much lower than that of the running buffer, thus resulting in an enhanced electric field at the injection end, and forming a field-*amplified* sample stacking technique, which can effectively improve the sensitivity.

2.2. Apparatus

The CE-ECL system (Xi'an Remax Electronic Co., Ltd., Xi'an, China) consisted of a high-voltage power supply (0–20 kV), an electrochemical potentiostat, an ECL collector, and a data processor. A conventional three-electrode system was employed with a 500 μm diameter Pt disk working electrode, a Pt wire counter electrode and a Ag/AgCl reference electrode. The photomultiplier tube positioned under the detection cell was biased at 800 V. The detection solutions consisted of 500 μL 100 mM phosphate buffer with an appropriate amount of $Ru(bpy)_3^{2+}$ which was refreshed every 2 h during experiments in order to maintain the reproducibility of the detection results. Prior to use, the electrode was scanned in 1.0 M H_2SO_4 within a potential range between −0.2 and 1.35 V (*vs.* Ag/AgCl) until a cyclic voltammogram characteristic of a clean Pt electrode was obtained.

A 45-cm length of uncoated fused-silica capillary (50 μm i.d., 360 μm o.d.) was used for the separation (Yongnian Optical Fiber Factory, Hebei, China). Before its first use, the capillary was flushed with 0.1 M NaOH overnight. Between runs, the capillary was treated with H_2O, 0.1 M NaOH, H_2O and running buffer each for 5 min, respectively. Electrokinetic sample injection was performed at 10 kV for the desired time.

2.3. Experimental design

Various multivariate experimental designs were adopted in CE analysis and central composite design was the most efficient one [32]. This design presented a good choice because of its high efficiency in investigating linear terms, the quadratic terms and the interaction effect of the studied factors [17]. In this study, a five-level central composite design was applied for investigating the influence of three significant variables on CE-ECL analysis. Each variable varied at five levels, and they were designated as $+\alpha$, +1, 0, −1, and $-\alpha$, respectively (Table 1). The resulting experimental matrix was detailed in Table 2. The matrix had 20 rows (each row corresponding to a CE experiment) and 4 columns (the first 3 columns corresponding to the 3 factors, and the fourth one corresponding to the response variable values). In this design, the star points were located at a distance ($\alpha = 1.68$) from the design center point to establish the rotatable condition, thus equally generate information in all directions [32]. Moreover, 20 runs were carried out in a randomized sequence to minimize the effect of uncontrolled variables on the response.

Just like the functions for evaluating chromatographic separation quality, a global criterion expressed as response function must be introduced to assess the CE separation quality. This kind of response function should define all the resolution between peaks and the migration time of last eluted analyte. The chromatography resolution statistic function (CRS function, Eq. (1)) proposed by Schlabach and Excoffler [36] can meet these requirements. In this study, the single response (CRS function) was chosen as the response function and its expression was:

$$\mathrm{CRS} = \left\{ \sum_{i=1}^{n-1} \left[\frac{(R_{i,j+1} - R_{opt})^2}{(R_{i,j+1} - R_{\min})^2 R_{i,j+1}} \right] + \sum_{i=1}^{n-1} \frac{R_{i,j+1}^2}{(n-1)R_{av}^2} \right\} \frac{t_n}{n} \qquad (1)$$

Table 1
Coded and actual values of variables of the central composite design model.

Variable	Actual values	Coded values	Real values of coded levels				
			$-\alpha$ (−1.68)	−1	0	1	$+\alpha$ (1.68)
Buffer pH value	x_1	X_1	1.4	2.5	4.0	5.5	6.48
Buffer concentration	x_2 (mM)	X_2	42.68	50	60	70	77.32
Voltage	x_3 (kV)	X_3	10.67	12.5	15	17.5	19.33

Here, $R_{i,j+1}$ and R_{av} are the resolution between consecutive peaks and the average resolution of all peaks, respectively, R_{opt} and R_{min} are the desired resolution (1.5) and the minimum acceptable resolution (1.0), respectively, t_n is the migration time of the last eluting solute and n is the number of compounds. A high CRS^{-1} value (the inverse of the CRS) indicates a well resolved electropherogram, therefore, CRS^{-1} value was optimized to a maximum value which took into account the maximum resolution and efficiencies with the minimum analysis time [36,37].

In summary, the experimental data was processed using Design Expert 7.0.0 software (Stat-Ease, Inc.), which involved in three stages for central composite design, namely, the coefficients for the regression model of different responses were estimated by Design Expert software, and the equation models could be built accordingly. Then analysis of variance (ANOVA) was conducted to test the significance of the fit to the second-order polynomial equation and their individual terms for the experimental data [22]. A factor was considered statistical significant in which the larger F value and the lower probability value (p value < 0.05, at the 95% confidence level), the more significant the corresponding terms. Eventually, the accuracy of the generated model was verified by comparing the values predicted by the model with the experimental results [16,37].

Following above analysis procedures, a quadratic regression model selected based on a multiple linear regression to define the relationship between the responses and the variables [38,39]:

$$\hat{Y} = b_0 + \sum_{i=1}^{n} b_i x_i + \sum_{i=1}^{n} b_{ii} x_i^2 + \sum_{i=1}^{n} b_{ij} x_i x_j + \xi \quad (i = 1\text{–}3, \quad j = 1\text{–}3) \tag{2}$$

where $\hat{Y}$ represents the response (CRS^{-1}), x_i are the studied factors, n is the number of factors (n = 3, buffer pH, buffer C and voltage in this study), and b_0, b_i, b_{ii}, b_{ij}, ξ are the intercept, linear, quadratic, interaction coefficients and the statistical error, respectively.

Table 2
Design matrixes generated for central composite design and the obtained response values.

Buffer pH (coded value)	Buffer concentration (coded value)	Voltage (coded value)	CRS^{-1}
5.5 (+1)	70 (+1)	17.5 (+1)	0.00729
2.5 (−1)	70 (+1)	17.5 (+1)	0.027
5.5 (+1)	50 (−1)	17.5 (+1)	0.00059
2.5 (−1)	50 (−1)	17.5 (+1)	0.031
5.5 (+1)	70 (+1)	12.5 (−1)	0.0099
2.5 (−1)	70 (+1)	12.5 (−1)	0.041
5.5 (+1)	50 (−1)	12.5 (−1)	0.0086
2.5 (−1)	50 (−1)	12.5 (−1)	0.0465
1.4 ($-\alpha$)	60 (0)	15 (0)	0.0392
6.6 ($+\alpha$)	60 (0)	15 (0)	0.00225
4.0 (0)	42.68 ($-\alpha$)	15 (0)	0.0366
4.0 (0)	77.32 ($+\alpha$)	15 (0)	0.0368
4.0 (0)	60 (0)	10.67 ($-\alpha$)	0.012
4.0 (0)	60 (0)	19.33 ($+\alpha$)	0.00096
4.0 (0)	60 (0)	15 (0)	0.027
4.0 (0)	60 (0)	15 (0)	0.0299
4.0 (0)	60 (0)	15 (0)	0.0296
4.0 (0)	60 (0)	15 (0)	0.0311
4.0 (0)	60 (0)	15 (0)	0.0274
4.0 (0)	60 (0)	15 (0)	0.0272

3. Results

3.1. Selection the key variables and their respective range

The main variables involved in CE separation include detection potential, sample injection time, Tris–H_3PO_4 buffer pH value, buffer concentration, separation voltage and temperature. Identifying the key variables affecting on the CE separation and their experimental region were vital for subsequent optimization. According to the previous report [33], the effect of temperature within the range permitted was insignificant for the CE separation and was kept constant at room temperature. Hence, the investigations of other variables on the separation using the classical single factor method were performed shown in supporting information (Figs. S1–S5). These investigations indicated that three variables (separation voltage, Tris–H_3PO_4 buffer pH value and buffer concentration) (Figs. S1–S3) showed significant effects on the separation and they were considered within a central composite design with their respective ranges summarized in Table 1. On the contrary, the variables (detection potential, sample injection time) were shown insignificant effects on the separation and were kept constant. And their values were set according to the following consideration: from Fig. S4, we can learn that a higher detection potential (>1.15 V) did not bring any significant improvement in the resolution but a higher background noise. Considering the high sensitivity (Figs. 2 and 3) and the separation performance (Fig. S4), we selected the optimal detection potential as 1.15 V. From Fig. S5, although the separation at 10 kV for 5 s was better than at 10 kV for 10 s, ECL signal at 10 kV for 5 s was rather weak; taking into account the resolution and the responses signals, the sample injection was at 10 kV for 10 s.

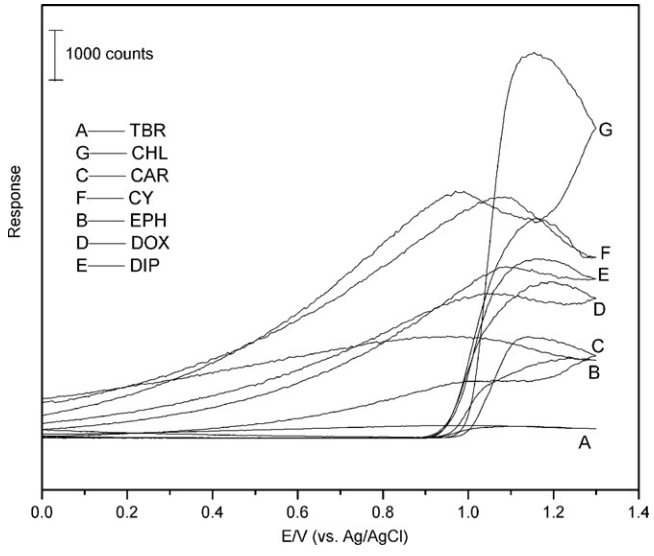

Fig. 2. ECL intensity–potential curve: (A) 5 mM $Ru(bpy)_3^{2+}$ in 100 mM phosphate buffer at pH 8.0; (B) 50 μM EPH in (A); (C) 50 μM CAR in (A); (D) 50 μM DOX in (A); (E) 50 μM DIP in (A); (F) 50 μM CY in (A); (G) 50 μM CHL in (A). Working electrode, 500 μm-diameter Pt electrode; scan rate, 100 mV s^{-1}, PMT, 800 V.

Table 3
ANOVA parameters for CRS^{-1}.

Source	Sum of squares	DF	Mean square	Coefficient estimate	*F* value	*p*-Value prob > *F*
Model	3.872E−003	9	4.303E−004	0.029	47.98	<0.0001
A-pH	2.395E−003	1	2.395E−003	−0.013	267.09	<0.0001
B-buffer C	9.505E−008	1	9.505E−008	−8.24E−005	0.011	0.92
C-voltage	2.507E−004	1	2.507E−004	−4.232E−003	27.95	0.0004
AB	3.828E−005	1	3.828E−005	2.188E−003	4.27	0.0657
AC	4.456E−005	1	4.456E−005	2.36E−003	4.97	0.0499
BC	5.951E−006	1	5.951E−006	8.625E−004	0.66	0.4343
A^2	1.084E−004	1	1.084E−004	−2.623E−003	12.09	0.006
B^2	1.150E−004	1	1.150E−004	2.702E−003	12.82	0.005
C^2	8.559E−004	1	8.559E−004	−7.372E−003	95.44	<0.0001
	R^2		0.9774	R^2_{adj}		0.9570
	Pred R^2		0.8494	Adeq precision		21.74

R^2: coefficients of determination that totally explain the variance in the data; Pred R^2: measures of how well the model will predict the responses for a new experiment; Adeq precision: measures of signal-to-noise ratio.

3.2. Data analysis

The coefficients (coded value) for the mathematical models were calculated by means of Design Expert 7.0.0 software and displayed in the 5th column of Table 3. The obtained model was described as follow (actual value):

$$\begin{aligned} CRS^{-1} = {} & 0.0065 - 1.76 \times 10^{-2}\ \text{buffer pH} - 4.35 \times 10^{-3}\ \text{buffer C} \\ & + 2.9 \times 10^{-2}\ \text{voltage} + 1.46 \times 10^{-4}\ \text{buffer pH} \times \text{buffer C} \\ & + 6.29 \times 10^{-4}\ \text{buffer pH} \times \text{voltage} + 3.45 \times 10^{-5}\ \text{voltage} \\ & \times \text{buffer C} - 1.17 \times 10^{-3}\ \text{buffer pH}^2 + 2.7 \times 10^{-5}\ \text{buffer C}^2 \\ & - 1.17 \times 10^{-3}\ \text{voltage}^2 \end{aligned} \quad (3)$$

By applying analysis of variance (ANOVA), the statistical significance of each effect was validated. If *p*-value (probability of the null hypothesis) was below 0.05, then the effect of that factor was statistical significant. The ANOVA results (Table 3) showed that two linear terms (buffer pH, buffer C), three quadratic terms (buffer C^2, buffer pH^2, $voltage^2$) and the interaction term of buffer pH with separation voltage were significant terms in the CRS^{-1} model.

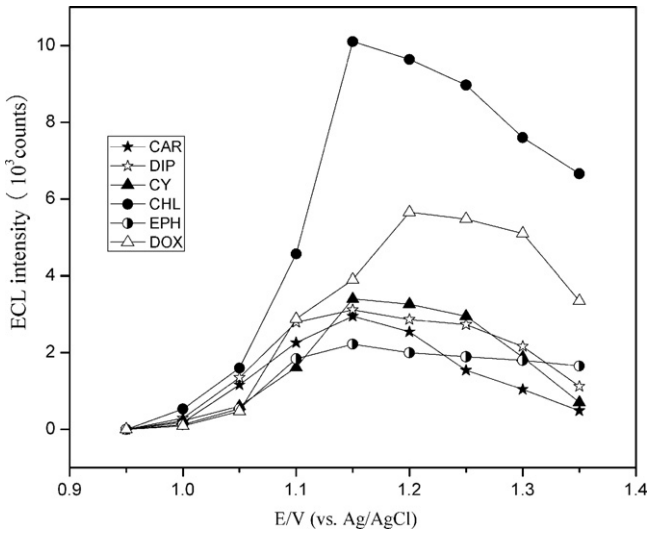

Fig. 3. Hydrodynamic voltammograms of 50 μM CAR (⋆), CHL (●), CY(▲), DIP(☆), DOX (△) and EPH (◑) at the 500 μm Pt electrode. CE-ECL conditions: separation capillary, 45 cm length (50 μm i.d., 360 μm o.d.); sample injection, 10 kV × 10 s; separation voltage, 17.5 kV; running buffer, 10 mM phosphate buffer (pH 8.0); 100 mM phosphate buffer (pH 8.0) containing 5 mM $Ru(bpy)_3^{2+}$ in ECL detection cell; PMT, 800 V.

And this interaction term cannot be determined by the traditional optimized method, indicating that the multivariate experimental design procedure was indispensable.

On the other hand, a high coefficient of determination (R^2, 0.97) was obtained, showing a reasonably good fitting of the experimental data (97%). Table 3 also showed that the predicted coefficients R^2 (0.85) was in reasonable agreement with R^2_{adj} (0.957) for CRS^{-1}, which indicates a good relationship between the experimental data and the fitted model.

4. Discussion

4.1. Optimal process

Based on the obtained quadratic model, the response surface can be explored graphically, which was plotted against two experimental factors while the third was held at center levels [28]. That way, three response surface plots of CRS^{-1} for CE-ECL analysis of the six antihistamines were depicted (Fig. 4a–c). For example, keeping the separation voltage at 15 kV, the CRS^{-1} response plotted vs. buffer pH and concentration (Fig. 4a), which showed a downtrend along the buffer pH axis (from 2.5 to 5.5), indicating the negative effect of buffer pH on the CE separation. At low pH value, the EOF flow rate was much slow and the six antihistamines could be fully ionized (positive charge), resulting in the difference in their electrophoresis mobility and an effective separation [28]. Across buffer concentration axis, the plot showed a quadratic effect curvature with the curve passing through a minimum value at around 60 mM. Thus, the response optimal region appears either at a low or a high buffer concentration at low pH value.

Fig. 4b was the effect of separation voltage and buffer pH on CRS^{-1}. A lower buffer pH value resulted in a higher CRS^{-1} value. The surface plot also illustrated a curvature along separation voltage axis and its corresponding curves passed through a maximum at middle region.

Fig. 4c represented the interaction between separation voltage and buffer concentration. Separation voltage showed a stronger degree of curvature with the maximum response at middle region, indicating separation voltage is a crucial factor to CE separation, which was consistent with the ANOVA results for CRS^{-1} (Table 3). This potential optimal zone appears to be at a separation voltage around 15 kV with an appropriate buffer concentration. Considering high separation resolution and short analysis time, the highest CRS^{-1} was chosen as optimization criterion. In this way, the optimum CE-ECL separation condition was generated from the central composite design model: 24.2 mM of buffer concentration, pH 2.7 and separation voltage of 15.9 kV (Table 4). Under the optimum conditions, the six antihistamine drugs were well separated in less than 22 min (Fig. 5a).

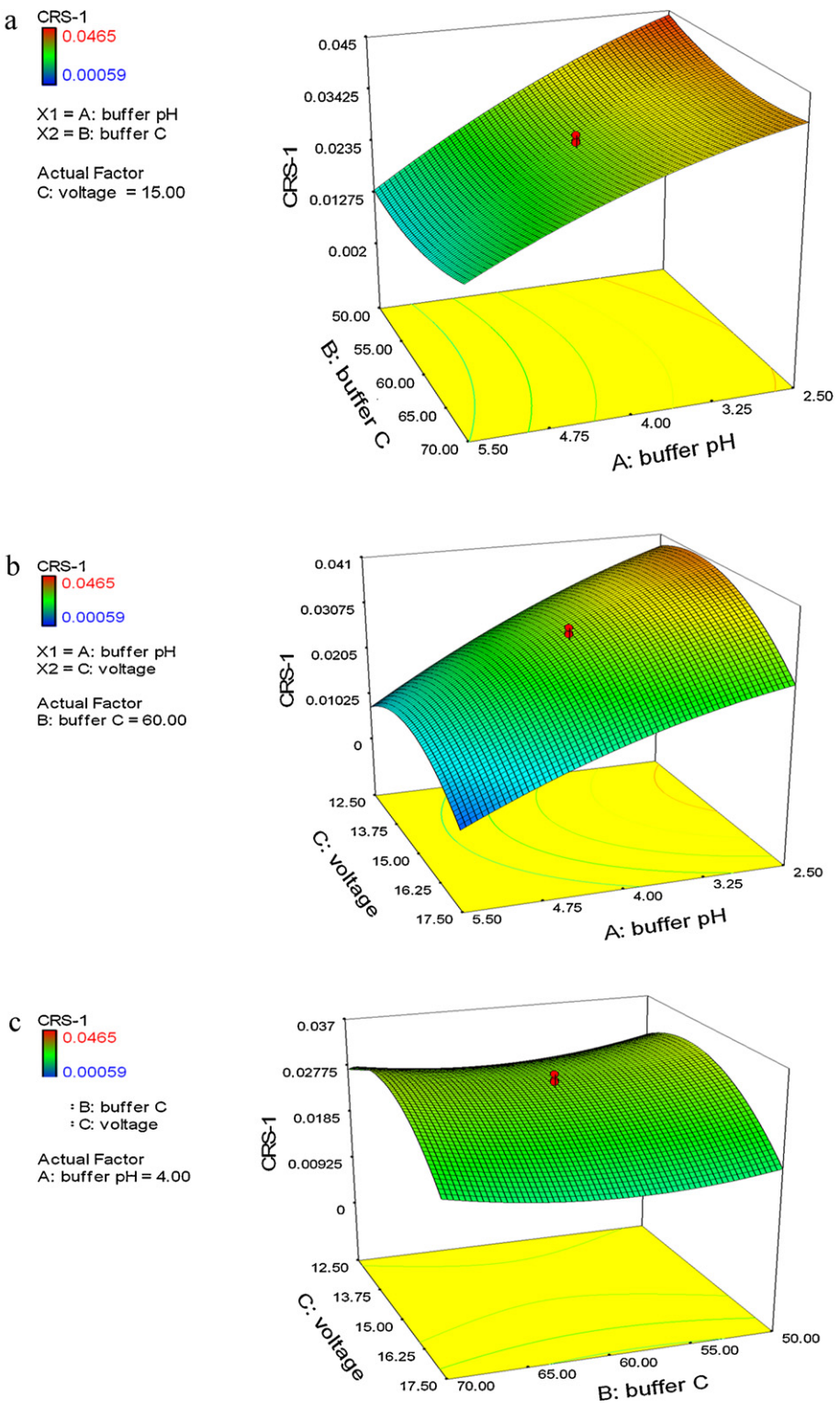

Fig. 4. 3D surface and contour plot for the six investigated drugs (CRS^{-1}): CHL, EPH, DIP, DOX, CAR, CY, as function of Tris–H_3PO_4 buffer concentration, buffer pH value and separation voltage.

4.2. Model verification

To verify the accuracy of this model, the experimental results were compared with the predicted values. Close agreement (Table 4) for the CRS^{-1} value (RSDs = 3.86%) could be obtained between the observed and the predicted values, illustrating the applicability of central composite design in the optimization of CE separation.

The precision of the method was tested by intra- and inter-day variations. The RSD of the ECL response and the migration time for intra- ($n = 5$) and inter-day ($n = 5$) were less than 4.8% and 5.8%, respectively.

Furthermore, the proposed CE-ECL technique was also employed to determine the six antihistamine drugs in human urine samples. In this study, the urine sample from a healthy female volunteer was diluted by 40-fold and then filtrated before analysis.

Table 4
Observed and predicted response for testing of the predictability of the model.

The best separation conditons from central composite design	Value
Tris buffer concentration (mM)	24.2
Tris buffer pH	2.7
Separation voltage (kV)	15.9
Perdited value (CRS^{-1})	0.0751
Experimental value (CRS^{-1})	0.0722
RSD%	3.86

Fig. 5 shows electropherograms of (a) standard mixed solution of six antihistamine drugs; (b) 40-fold diluted blank urine sample; (c) 40-fold diluted urine spiked with the mixed standard solutions. The satisfactory results were obtained without significantly sacrificing the separation resolution in Fig. 5c.

In addition, a comparison of the results obtained by this method with other chromatography methods was carried out (data not shown). In summary, although the detection limit (0.01–0.08 μg/mL) for all studied drugs obtained by this method was higher than MS detection [2,5,7–11], it still can be comparable with UV detection [6,13,15,20,22]. The obtained linear ranges were equivalent or better than the mentioned chromatography methods.

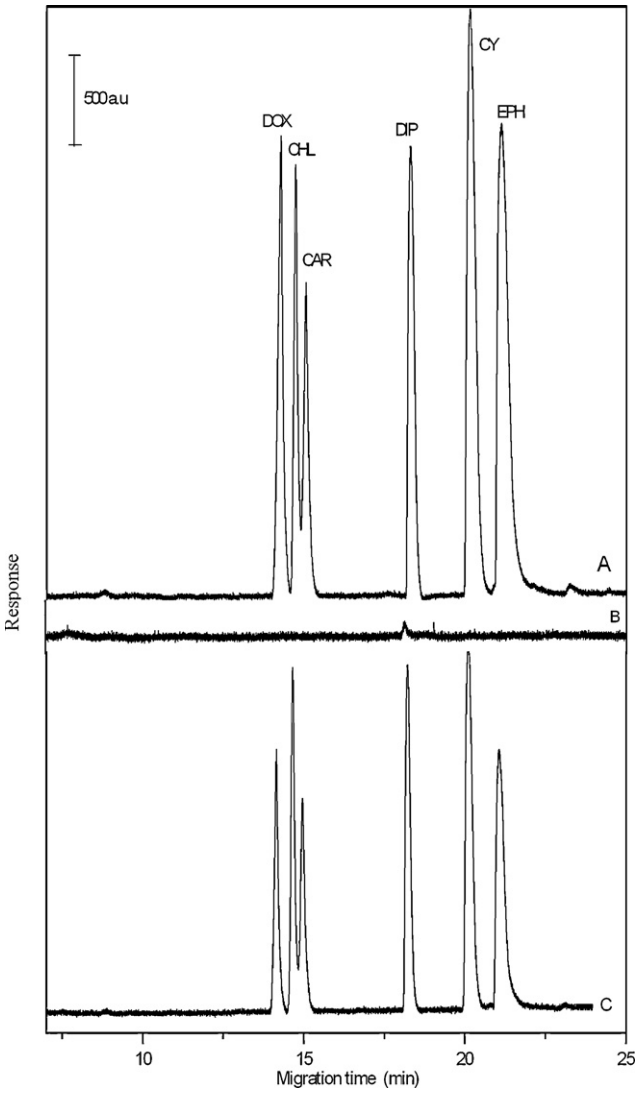

Fig. 5. Typical electropherograms of (A) CHL (20 μM), EPH (60 μM), DIP (40 μM), DOX (40 μM), CAR (60 μM), CY (40 μM) mixed standard solutions; (B) 40-fold diluted blank urine sample, (C) 40-fold diluted urine spiked with CHL (10 μM), EPH (30 μM), DIP (20 μM), DOX (20 μM), CAR (30 μM), CY (20 μM) mixed standard solutions; separation conditions, 24.2 mM Tris–H_3PO_4 pH 2.7–15.9 kV separation voltage; sample injection, 10 s at 10 kV; detection potential, 1.15 V; 100 mM phosphate buffer (pH 8.0) containing 5 mM $Ru(bpy)_3^{2+}$ in ECL detection cell; PMT, 800 V.

A main difference between our manuscript and already published paper was that we introduced the chemometric experimental design (central composite design) based optimization techniques to the CE separation. The chemometric methodology involved the simultaneous investigation of the selected experimental factors with an adapted design of experiments allowing high quality information from a relatively limited number of measurements. As a consequence of that, the optimization procedure for multi-component analysis can be greatly simplified. Moreover, the interaction effects among the experimental factors are included, indicating that this multivariate experimental design procedure was indispensable.

In addition, single factor method provides a local knowledge, meaning that only the results of the experiments actually performed could be known. In contrast, from the results obtained by the experimental design, a simple mathematical model could be obtained. It can provide good predictions over the entire experimental space thus enable guiding the CE separation better.

5. Conclusion

It is concluded that central composite design is very useful for rapid optimizing CE-ECL analysis conditions with an acceptable resolution and reasonable time. Compared to traditional methods, central composite design can greatly simplify the optimization procedure for multi-component analysis. Moreover, the interaction effects among the experimental factors are included indicating that this multivariate experimental design procedure was indispensable. In addition, central composite design can provide good predictions over the entire experimental space, which is capable of guiding the CE separation better. The developed CE-ECL system has been validated as a rapid, sensitive, accurate, and reproducible method, and was successfully employed in urine sample analysis.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.talanta.2011.10.040.

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