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Kinetic-Potentiometric Determination of Paracetamol and *p*-Aminophenol Using Partial Least Squares and Principal Components Regression Methods

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Abstract-Partial least squares (PLS) regression and principal component regression (PCR) multivariate calibration methods have been applied for the simultaneous determination of paracetamol (PAR) and *p*-aminophenol (PAP) using kinetic data obtained by novel potentiometric method. The method is based on the rate of chloride ion production in reaction of PAR and PAP with N-chlorosuccinimide (NCS) which is monitored by a chloride ion-selective electrode. The production rate of chloride ions in the reaction of PAR and PAP with NCS is different so that PLS and PCR can be applied to analyze the experimental potentiometric data. The determination of PAR and PAP is performed in the concentration ranges of 0.50-65.0 and 0.10-75.0 μg mL^{-1}, respectively. The total relative standard errors in PLS and PCR methods were calculated to be 4.07 and 4.74 for PAR and 3.93 and 4.79 for PAP, respectively.

Keywords-Kinetic-Potentiometric determination, Paracetamol, *p*-Aminophenol, Partial least squares, Principal component regression

1. INTRODUCTION

Paracetamol (PAR) or acetaminophen is an extensively administered antipyretic and analgesic for treating the symptoms of different painful processes [1,2]. It belongs to mild analgesics group of drugs in the analgesic-antipyretics sub-group. It is interesting that the discovery of PAR as an effective antipyretic and analgesic in the mid-1940s led to a breakthrough in the pharmaceutical area in relation to other substances used for the same purpose [3]. The most common dosage forms for PAR are tablets, drops, suspensions and syrups. PAR in tablet form is stable under normal conditions, but under abnormal conditions such as high temperature and humidity, PAR degrades slowly forming a mixture of contaminants such as acetic acid and *p*-aminophenol (PAP) [4]. PAP is the hydrolytic product of acetaminophen and is reported to have significant nephrotoxicity and teratogenic effects and has been detected in PAR as an impurity or synthetic intermediate [5,6]. Furthermore, the industrial synthesis of PAR occurs through the acetylation of PAP with acetic anhydride [7]. Due to the discoveries of significant nephrotoxicity and teratogenic effects of PAP, its maximum content in pharmaceuticals is limited to 50 ppm by the European [8] and United States [9] pharmacopeia.

Chromatographic methods have been used for the determination of PAP in PAR formulations [10-13]. Spectrophotometric techniques using chemometric methods for data analysis have also been reported for the simultaneous determination of PAR and PAP [14,15]. Electrochemical methods of analysis such as voltammetric and potentiometric techniques are widely used as efficient methods for the trace determination of pharmaceuticals [16-20]. So, it is interesting for the electrochemists to design novel electrochemical methods for the determination of traces of pharmaceuticals in their formulations by introducing new electrode materials as well as methods of experimental data analysis. Kinetic determination of PAR has also been reported by several workers [21,22]. A large number of papers have been published and presented on PAR quantification. This shows the importance of this compound. A valuable review has been published on PAR determination in which the methods of analysis have been classified, summarized and discussed the different proposed methods for the determination of PAR, alone and in mixtures, in formulations and biological samples [23].

Perhaps the main improvement in simultaneous determination of species in the same mixture without separation is using multivariate calibration methods. These methods such as principal component regression (PCR), partial least squares (PLS) regression and artificial neural networks (ANNs) have recently been extensively used and applied for the simultaneous determination of analytes having the same chemical properties that cannot be resolved with common methods [24-27]. Partial least squares (PLS) and principal component regression(PCR) methods have attracted the interest of many researchers in the field of chemistry as powerful chemometric methods for multivariate calibrations as well as for the

extraction of more information from experimental data in various areas of analytical chemistry [26,27].

This work reports the application of PLS and PCR multivariate calibration methods for the simultaneous kinetic-potentiometric determination of binary mixture of PAR and PAP using chloride ion-selective electrode. The method is based on the differences observed in the rate of production of Cl^- in the reaction of N-chlorosuccinimide (NCS) with PAR and PAP. During the reaction of PAR and/or PAP with NCS, Cl^- anion is produced and its concentration is potentiometrically determined by chloride ion selective electrode. PLS and PCR regression methods were then applied to analyze the experimental data.

2. EXPERIMANTAL

2.1. Chemicals

All chemicals were of analytical reagent grade and double distilled water was used throughout. The stock solution of PAR (1000 µg mL^{-1}) was prepared in a 100-mL flask by dissolving 100.0 mg of paracetamol (purchased as analytical grade from DarouPakhsh Co., Tehran, Iran) in water and diluting with water to the mark. The stock solution of PAP (500 µg mL^{-1}) was also prepared in a 100-mL flask by dissolving 50.0 mg of p-aminophenol (Fluka) in water and diluting with 0.01 M H_2SO_4 to the mark. PAP solution in water (not in acidic medium) is stable for few days in refrigerator. So, it was preferred to prepare its stock solution in acidic medium. These solutions are fairly stable at least for a month in refrigerator. The stock solution of 0.05 M N-chlorosuccinimide (NCS, Merck) was prepared in a 100-ml flask by dissolving 0.6667 g of NCS in water and diluting to the mark. This solution was prepared daily and kept in refrigerator. Acetate buffer solution (0.1 M, pH 4.5) was prepared using acetic acid and NaOH solutions and adjusting its pH with a pH-meter. The changes in the potential of the chloride selective electrode immersed in the reaction vessel were recorded during 100 s with 1s intervals.

2.2. Apparatus and Software

A solid-state chloride selective electrode (Metrohm Model 6.0502.120) was used in conjunction with a double junction Ag/AgCl reference electrode (Metrohm Model 6.0726.100) whose outer compartment was filled with a 10% KNO_3 solution. The Metrohm Model 780 potentiometer, attached to a computer, was used for recording the kinetic potentiometric data. All measurements were carried out in a thermostated (25±0.2°C), double-walled reaction cell with continuous magnetic stirring. The electrode was stored in 1.0×10^{-3} M potassium chloride solution after use. For pH measurements, a Metrohm Model 780 pH-meter with a combined glass electrode was used. PLS and PCR analysis were performed using PLS and PCR toolboxes in MATLAB 7.0 program.

2.3. Procedure

25.0 mL of doubly distilled water, 2.0 mL of acetate buffer solution, pH 4.5 and 10.0 mL of the standard or sample solution of PAR and/or PAP were transferred into a thermostated(25.0 ºC) reaction cell with stirring and the electrodes were immersed into the solution. After the stabilization of the potential, the recorder was started and 1.0 mL of 5×10^{-2} M NCS solution was injected into the cell. The potential changes versus time were recorded at the time intervals of 1s. A synthetic set of 32 solutions including different concentrations of PARand/or PAP (24 solution as calibration set and 8 solutions as prediction set) was prepared in the concentration ranges of 0.5-65.0 and 0.1-75.0 μg mL^{-1}, respectively (Tables 1 and 2). Data were mean-centered before being input to the appropriate algorithms.

3. RESULTS AND DISCUSSION

Determination of pharmaceuticals having reducing properties that can be oxidized with inorganic and organic oxidizing agents has been extensively reported by several workers. Most of these methods have been reported as kinetic methods of analysis and some others as common complexometric methods. In this report, NCS plays a prominent role. Acting as an oxidant, NCS oxidizes PAR and/or PAP and during the oxidation reaction, chloride ion is produced kinetically with different rates in the reaction of NCS with PAR and PAP. However, there is not any report on simultaneous determination of PAR and PAP based on the above reaction.

3.1. Optimization of the experimental parameters

At first, the potentiometric characteristics of the commercial chloride selective electrode in the acetate buffer solution were studied. Typical calibration graph for the chloride selective electrode, i.e. potential (E) *vs*. log(a_{Cl^-}), showed a linear response in the range of 3.0×10^{-6} M to 0.1 M of chloride ion concentration with the regression coefficient of 0.9992. The slope of the E-log(a_{Cl^-}) curve was found to be 58.4±0.4 mV/decade and remained almost constant during this study. The fast response of the electrode and its Nernstian behavior with respect to chloride ion indicates that the electrode can be employed effectively in kinetic studies of the above-mentioned reaction.

3.1.1. Effect of NCS concentration

The effect of NCS concentration on the reaction rate of PAR and/or PAP was investigated in detail. In order to get the pseudo-first order reaction condition, the concentration of the agent (here, NCS) should be high in comparison with the analytes (here, PAR and PAP). So, the effect of NCS concentration on the reaction rates of both species was studied in the range of 5×10^{-4} M to 5×10^{-2} M of NCS. The concentration of PAR and PAP was 1.0×10^{-5} M. Further increase in the oxidizing agent concentration was not applicable due to the limited

solubility of NCS in water. Increase in NCS concentration caused increase in the reaction rate of both species. Therefore, to have the best sensitivity in the determination, 5×10^{-2} M NCS was selected as the optimum concentration for further studies

3.1.2. Effect of pH

The effect of pH on the reaction rates of both species with NCS over the pH range of 2.0 to 9.0 was examined. In highly acidic or basic media, NCS can liberate chloride ion slowly. By immersing the chloride ion selective electrode in acidic or basic NCS solution, the potential of the electrode is changed showing liberation of chloride ion. With increase in pH of the solution, the reaction rate of PAR and PAP with NCS is slightly increased in the pH range of 2.0 to 4.5 and remain constant up to pH 9.0. However, the maximum difference in kinetic behavior of PAR and PAP was observed at pH 4.5. So, pH of 4.5 was selected as the optimized pH for further studies.

3.2. Kinetic reaction of PAR/PAP with NCS

Fig. 1A shows the potential-time behavior of the reaction of NCS with PAR and PAP and their mixture at the optimized conditions. As it is clear, the reaction rate of PAR with NCS is faster than that of PAP and almost finished at 60 s. This difference in the reaction rates allowed us to design PLS and PCR methods for the simultaneous determination of PAR and PAP. Fig.1B shows typical reaction curves for the reaction both species with NCS at different concentrations of PAR and PAP in their mixtures.

3.3. Multivariate calibration methods and statistical parameters

Partial least squares regression (PLS), being a projection method, is one of the most popular methods in chemometrics. PLS is based on the latent variables (LV's). The power of PLS is due to the fact that LV's simultaneously describe the maximum predictive variance of a block, and provide maximal fit to the path model [28]. In the PLS regression, a relationship is sought between response(s) **Y** (or dependent variable (s)), and data matrix **X** (independent variable(s)). Latent variables $\mathbf{T}_x$ are extracted both to model **X** and to correlate with **Y**. The detailed descriptions on PLS and different available algorithms in PLS can be found in the literature [29,30].

The first step in the simultaneous determination of species by PLS and PCR methodologies involves constructing the calibration matrix for the binary mixtures of PAR and PAP. Table 1 shows the composition of calibration set randomly designed for the determination of PAR and PAP ($\mu g\ mL^{-1}$) using PLS and PCR methods.

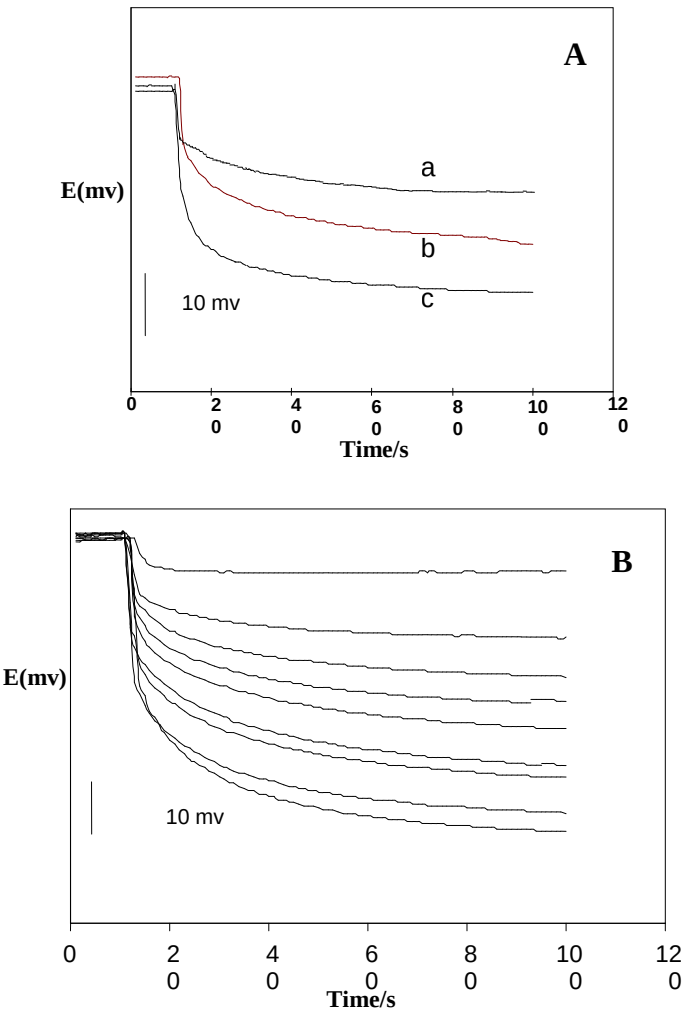

Fig. 1. A: Potential-time curves for the reaction of NCS with (a) 5 μg mL^{-1} of PAR, (b) 10 μgmL^{-1} of PAP, and (c) their mixture at pH 4.5, acetate buffer solution. NCS concentration is 5×10^{-2} M. **B:** Potential-time curves for the reaction of NCS with different concentrations of PAR and PAP

Table 1. Composition of the calibration set randomly designed for PLS and PCR method in the determination of PAR and PAP (μg mL^{-1})

Sample	PAP	PAP	Sample	PAR	PAP
1	1.0	0.5	13	8.0	35.0
2	20.0	10.0	14	8.0	35.0
3	40.0	30.0	15	8.0	35.0
4	10.0	1.0	16	15.0	40.0
5	30.0	20.0	17	15.0	40.0
6	55.0	40.0	18	15.0	40.0
7	20.0	10.0	19	25.0	45.0
8	40.0	40.0	20	25.0	45.0
9	65.0	55.0	21	25.0	45.0
10	0.5	10.0	22	30.0	55.0
11	30.0	20.0	23	30.0	55.0
12	55.0	40.0	24	30.0	55.0

The designed calibration model was validated with 8 synthetic mixture sets containing considered analytes i.e. PAR and PAP in different concentrations and proportions that were randomly designed (Table 2).

Table 2. Composition of experimental samples, their predicted values by PLS and PCR models and some calculated statistical parameters

Sample	Actual (μg mL^{-1})		Predicted (μg mL^{-1})				Recovery (%)			
	PAR	PAP	PCR		PLS		PCR		PLS	
			PAR	PAP	PAR	PAP	PAR	PAP	PAR	PAP
1	8.0	20.0	8.245	22.831	7.447	21.562	103.0	114.1	93.08	107.8
2	15.0	30.0	16.251	32.693	16.292	32.071	108.3	108.9	108.6	106.6
3	25.0	1.0	24.112	1.125	25.517	1.134	96.44	112.5	102.0	113.4
4	30.0	55.0	29.698	58.428	29.105	53.723	98.99	106.2	97.01	97.6
5	35.0	10.0	35.139	10.452	36.182	12.015	100.3	104.5	103.3	120.1
6	40.0	65.0	38.208	64.854	38.429	61.983	95.52	96.69	96.07	95.3
7	45.0	0.5	42.974	0.542	43.876	0.573	95.49	108.4	97.5	114.6
8	55.0	40.0	52.734	40.643	52.195	38.769	95.88	109.1	94.9	96.9
Recovery (%)							99.24	107.54	99.057	106.537
RSE (%)							3.931	4.797	4.069	4.743

To select the number of factors in PLS algorithm, the leaving one out, cross-validation method [31], was employed. Here, PLS-2 modeling has been used and the prediction error sum of squares (PRESS) was calculated for both analytes and drawn against the number of factors:

$$PRESS = \sum_{i=1}^{m} \left(\hat{C}_i - C_i \right)^2 \qquad (1)$$

Where m is the total number of calibration samples, $\hat{C}_i$ represents the estimated concentration, and C_i is the reference concentration for the ith sample left out of the calibration during cross validation. For finding the fewest number of factors, the F-statistic was also used to carry out the significant determination. Fig. 2 shows a plot of PRESS against the factors involved in the mixture of components. The optimum numbers of factors were 2 for both PAR and PAP in PLS modeling as well as for PCR modeling.

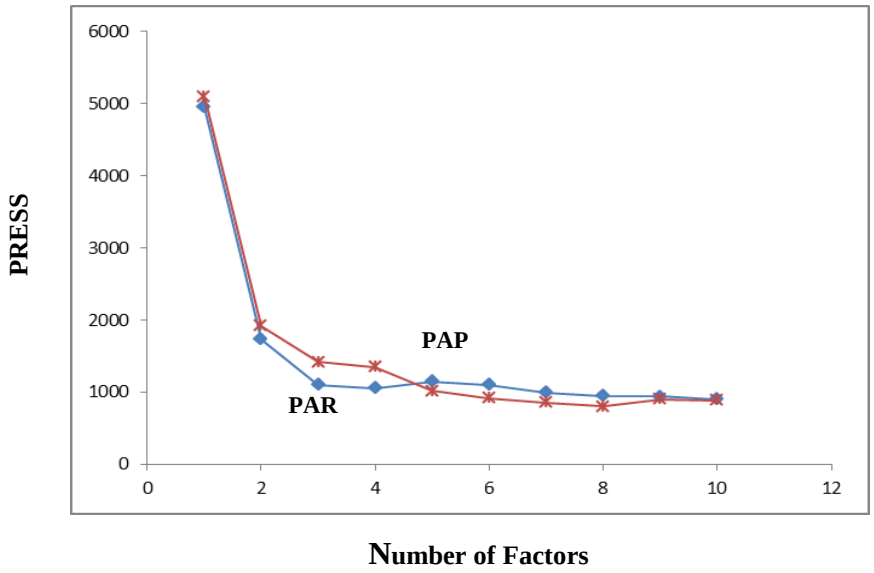

Fig. 2. Plot of PRESS versus the number of factors for PAR and PAP using PLS modeling

The validation step of PLS and PCR methodologies was carried out by running PLS and PCR on the prediction set. The obtained results are given in Table 2. The obtained results are quite acceptable for both analytes. The prediction error of a single component in the mixture is calculated as the relative standard error (RSE) of predicted concentration:

$$RSE(\%) = 100 \times \left(\frac{\sum_{j=1}^{N} (\hat{C}_j - C_j)^2}{\sum_{j=1}^{N} (C_j)^2} \right)^{1/2} \quad (2)$$

Where N is the number of samples, C_j the concentration of the component in the *j*th mixture and $\hat{C}_j$ the estimated concentration.

For the evaluation of the predictive ability of a multivariate calibration models, the root mean square error of prediction (RMSEP) and the relative standard error of prediction (RSEP) can be used.

$$RMSEP = \left(\sum_{i=1}^{N} \left(\hat{C}_i - C_i \right)^2 / n \right)^{1/2} \quad (3)$$

$$RSEP(\%) = \left(\sum_{i=1}^{N} \left(\hat{C}_i - C_i \right)^2 / \sum_{i=1}^{N} (C_i)^2 \right)^{1/2} \times 100 \quad (4)$$

The squares of correlation coefficient (R^2), which is an indication of the quality fit of all the data to a straight line [32] can also be calculated as:

$$R^2 = \sum_{i=1}^{N}\left(\hat{C}_i - \bar{C}\right)^2 / \sum_{i=1}^{N}\left(C_i - \bar{C}\right)^2 \quad (5)$$

Where, $\bar{C}$ is the mean of the true concentration in the prediction set. Table 3 shows values of RSEP, RMSEP and R^2 for each component using PLS and PCR. It is shown that the obtained values for the statistical parameters are almost the same for both PLS and PCR methods. So, no significant differences was obtained in the prediction errors by PCR and PLS. PLS almost require fewer latent variables than PCR, but this did not appear to influence predictive ability of PLS [33,34].

Table 3. Statistical parameters calculated for the prediction set using PLS and PCR methods

Component	RSEP (%)		RMSEP		R^2	
	PLS	PCR	PLS	PCR	PLS	PCR
PAR	4.068	3.931	1.415	1.368	0.8909	0.8727
PAP	4.742	6.773	1.697	2.424	0.9025	0.9838

3.4. Interference study

In order to assess the possible analytical applications of the proposed methods, the effects of common excipients used in pharmaceutical preparations were studied. Potential changes of a solution containing PAR (1.0 μgmL^{-1}) and PAP (1.0 μgmL^{-1}) were analyzed for four times. Afterwards, the effect of interfering species at different concentrations on the potential of this solution was studied. A species was considered interference when its presence produced a variation in the concentration of the species with more than 5% relative error. The following excipients did not interfere in the maximum tested concentrations (μgmL^{-1}) shown in parentheses: glucose (250.0), Tartaric Acid (100.0), methocarbamol (200.0), Phenacetin (50.0), caffeine (200.0). Some other compounds with significant redox properties (e.g., Ascorbic acid and salicylic acid) may interfere in the proposed procedure. The main goal of this research is the determination of PAR and PAP in acetaminophen tablets where the redox compounds are absent.

3.5. Real sample analysis

The proposed methods were applied for the simultaneous determination of PAR and PAP in several commercially available pharmaceutical formulations. Twenty tablets of each sample were accurately weighed and their solutions were prepared by dissolving them in water and filtering the solutions.

Table 4. Determination results of analytes in pharmaceutical samples including tablets (four replicates)

Sample	Nominal (μg mL^{-1})		Spiked (μg mL^{-1})		Found (μg mL^{-1})		Recovery (%)	
					PCR		PLS	
	PAR	PAP	PAR	PAP	PAR	PAP	PAR	PAP
1[a]	10.0	-	-	5.0	10.71 (107.1)	5.31 (106.2)	10.63(106.3)	5.27 (105.4)
2[a]	10.0	-	-	10.0	10.62 (106.2)	10.92 (109.2)	10.51(105.1)	10.45 (104.5)
3[a]	10.0	-	-	15.0	10.94 (109.4)	16.01 (106.7)	10.48(104.8)	16.64 (110.9)
1[b]	10.0	-	-	10.0	10.99 (109.9)	11.04 (110.4)	10.74(107.4)	10.96 (109.6)
2[b]	10.0	-	-	15.0	11.25 (112.5)	16.91 (112.7)	11.04(110.4)	15.93 (106.2)
RSE%					0.56	0.91		

[a]Acetaminophen (325 mg per tablet); Jalinous Lab., Tehran, Iran

[b] Adult cold tablet (325 mg per tablet); Dr. Abidi Co., Iran

Table 5. Comparison of the electroanalytical methods for the determination of PAR

Method	Linear range (μM)	Detection limit (μM)	Ref.
Amperometry Electrode: Polyphenol oxidase/glassy carbon paste electrode	Up to 70	7.8	35
Square wave voltammetry Electrode: CNT/GCE	1.0-100	0.25	36
Voltammetry Electrode: Perm-selective cellulose acetate membrane modified electrode	Up to 2000	100	37
Amperometry Electrode: Polyphenol oxidase-vaseline-graphite electrode	120-5800	88	1
Molecular imprinted polymer	5-500	0.79	38
Differential pulse voltammetry Electrode: Carbon ionic liquid electrode	1.0-2200	0.5	39
Differential pulse voltammetry Electrode: Nano-TiO2/polymer coated GCE	12-120	2.0	40
Potentiometry-kinetic Electrode: chloride ion selective electrode	3.3-430	0.8	This work

The prepared solutions containing PAR and PAP (spiked in the solutions) were analyzed (n=4) by the proposed methods. The quantitative results of the analysis are summarized in Table 4. The good agreement between these results and the nominal values labeled or the spiked values indicates the successful applicability of the proposed methods for the simultaneous determination of PAR and PAP in pharmaceutical samples.

4. CONCLUSIONS

A simple and sensitive analytical method has been developed for the simultaneous kinetic determination of paracetamol and *p*-aminophenol in pharmaceutical formulations, based on their different reaction rates with NCS. Partial least squares (PLS) and principal component regression (PCR) methods were applied for the simultaneous determination of the concentration of the analytes without their prior separation. The results indicate that both of the methods can appropriately model multicomponent systems and predict unknown analyte concentrations. Table 5 summarizes the electroanalytical methods for the determination of PAR from this study compared with other methods. It can be seen that the proposed provides a significant low detection limit, high sensitivity and wide linear range. The main advantages of the proposed method is its simplicity and its ability in determining lower concentrations of PAP in the presence of high amounts of PAR so that it can be successfully applied for the analysis of real samples.

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