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Research Article

Simultaneous Determination of Paracetamol-containing Tablets in Binary Mixtures by pH-Potentiometric Titration and Multivariate Calibration

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Abstract

Acid-base titration method is developed for the simultaneous determination of paracetamol "PAR" in the presence of ascorbic acid "ASC" or methionine "MET". A 50 ml solution of binary mixture of the cited components is titrated with 0.60 M NaOH in the presence of 0.1 M KCl and using automatic titrator, pH electrode and stirrer. The potentiometric measurements against the volume of NaOH are first intra/interpolated along the fixed pH range of 3 to 12.5 and then the linear relationship between the volumes of titrant and the concentrations of analytes is plotted. The designed models are then used to predict the concentrations of components in unknown samples either by simultaneous equations using Cramer's rule or by classical least squares CLS regression. Direct calculation and first derivative methods are also applicable for analysis of well separated titration steps of PAR and ASC. The concentration ranges applied successfully for the simultaneous determination of PAR, ASC and MET in pharmaceutical tablets are in order 35-250, 80-265 and 45-150 mg/ml. The relative errors of prediction for the two-component mixtures are 1.11% for PAR, 1.79% for ASC and 2.13% for MET.

.**Key words:** Paracetamole, Simultaneous determination, methionine.

Introduction

Acid-base potentiometric titration is the most common analytical technique for determining the concentration of one acid in solution. Dashek and Micales(1) presented a summary of procedures employed for the detection and quantification of organic acids. They reported their methods, capillary electrophoresis, calorimetry, conductimetric titration, differential pulse polarography, enzymatic methods, gas chromatography, high-pressure liquid chromatography, ion exchange chromatography with gradient elution, but did not consider a potentiometric titration. A generalization of this technique for a mixture of acids is very important. Kankare(2) proposed a simple linear relationship titration of mixtures and the mole fraction of the acids. He concluded that it is possible to determine by potentiometric titration the concentration of weak acids in a mixture. Betti et al (3) carried out a potentiometric titration of mixtures of two weak monoprotic acids.

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They found that the method precision is a function of dissociation constants and the ratio of the acid concentrations. Gordus(4) carried out similar experiments but using polyprotic acids. He concluded that it is impossible to determine, by potentiometric titration, the concentrations of the individual acids in a mixture. Papanastasiou et al (5) presented an iterative method for a potentiometric titration of a mixture of monoprotic weak acids and found that it is possible to obtain accurate results even for acids with similar dissociation constants.

Serious difficulties arise when complicated mixtures are analyzed and especially in the case of overlapping pK values. Using different graphical and numerical methods (6) many attempts are proposed to solve this problem in the last decades. It seems that mainly two computer-aided approaches are applied successfully to solve this issue. They are based on the so called *hard-* and *soft-modeling*.

The *hard-modeling* approach is founded on the strictly theoretical base, including precise treatment of mass balance equations (7; 8). The simultaneous determination of analytes by potentiometric titration is initiated by Gran (9), Gran (10) and Burns (11). They deduced a linear plot method for the simultaneous determination of halides and thiocyanate mixtures. However, the necessary hand-drawing procedures are time-consuming and are difficult to resolve complex systems. Meanwhile, the mathematical models they used are all based on the chemical thermodynamic equilibrium and accurate measurement of potential and accurate calibration of the electrode system is required. Furthermore, the knowledge of formation (or dissociation) constants is always needed.

The *soft-modeling* approach (12; 13; 14) is based on the similarity of behavior of successive pH-metric titrations of standard solutions with that analyzed solution. Multivariate calibration techniques are applied to potentiometric titration for determination of acid mixture (13). The techniques used a linear relationship between the volume of titrant added and the analytes concentration. The most widely used techniques, e.g., classical least square (CLS), inverse least square (ILS), principal component regression (PCR), partial least square (PLS) determined the amount of the compounds.

The present study is related to the *soft-modeling* approach.

The application of multivariate calibration to potentiometric titration data is introduced by Lindberg and Kowalski (13) in 1988 for the simultaneous determination of acid mixtures using PLS regression. In this method, the authors used the volumes needed to

reach a given pH as response data. They assumed a linear relationship between the volume of titrant added and analyses concentrations. After that, this PLS calibration method has been applied to acid–base titration(13), complex metric titration (15) and potentiometric precipitation titration (16) by different researchers.

The assumed linear relationship, however, becomes complicated in the complex acid–base systems and interactions between components in the titration vessel.

To overcome this problem, Song used ANN to treat potentiometric acid–base titration(17). However, this method has two restrictions yet:

(1) measuring the titrant volume to reach a pre-selected pH requires an automated titration system and the acid–base reaction must be completed rapidly; (2) in this method, a pH interval is selected and volume measurement is achieved for this interval. Meanwhile, the starting pH is dependent on the concentration of components in the calibration standards. The highest pH of the standard solution in which no titrant added is given as the starting pH. Therefore, the pH interval is narrowed in the presence of dilute solutions.

The use of pH at the different volumes of titrant added instead of volume as response data can solve this problem.

Paracetamol has a phenolic structure, while methionine and ascorbic acids contain mono- and dibasic carboxylic acids, respectively. Because of their acidic character, they are titrated by a base. Caffeine, on the other hand, is basic character and is excluded therefore from the present experiment.

Material and Methods

Chemicals and reagents

All chemicals are of HPLC-analytical grade and are used without further purification. Hydrochloric acid, potassium chloride and sodium hydroxide are purchased from BDH, UK. Paracetamol (acetaminophen) are prepared as reference standard by methanolic extraction from Paracetamol tablets (PARALIEF, ClonMedica, Irland) with melting point 260°C, methionine from Riedel-de Haen (Germany) and ascorbic acid from ANALAR, UK.

Pharmaceutical formulation

Commercial pharmaceutical samples of

- Panadol Extra tablets containing 500 mg PAR and 65 mg CAF (Teriak, Egypt)
- Hepamol tablets 500 mg PAR and 100 mg MET (Hikma,Egypt),
- Efferalgan Vitamin C effervescent 330 mg PAR and 220 mg ASC (UPSA,Tunisie)

are purchased from the local market.of EL-Beida (Libya)

Apparatus

Potentiometric measurements are carried out using (a Mettler Toledo burette, model DV-50) accurate to 0.01 ml. The indicator electrode is a Mettler Toledo combined pH electrode model DG111-SC. The potentiometric measurement is performed on a titration cell (50 ml) at room temperature (25°C).

The potentiometric data is analysed by a computer program written in Microsoft EXCEL 2007 for calculating the unknown concentrations using simultaneous equations (18) and classical least squares (19).

Potentiometric titration procedure

In a typical titration, a suitable amount of an individual drug agent or a mixture is dissolved in distilled water, then 5 ml 1 M KCl solution is added, transferred to a 50 ml measuring flask and completed to the mark with distilled water. The solution is placed in titration vessel, stirred and titrated with 0.250 M sodium hydroxide solution using automatic burette. The pH is recorded after each 0.02 ml addition of the titrant and the titration is continued up to 10 ml NaOH. For each solution, at least 60 data points are recorded.

Construction of Calibration Curves

Method I: Simultaneous equation method

For binary mixture of PAR and MET

The two potentiometric graphs of PAR and MET are overlain as shown in Figure 1. The calibration curves are constructed by plotting concentration versus volume of NaOH at pH 7.5 and pH 10. and the regression parameters of slope and intercept values of both these drugs are as shown in Figure 2 and presented in Table 1.

For binary mixture of PAR and ASC

The two potentiometric graphs of PAR and ASC are overlain as shown in Figure 4. The calibration curves are constructed by plotting concentration versus volume of NaOH at pH 7.5 and 10. as shown in Figure 5 and the regression parameters of slope and intercept values of both these drugs are presented in Table 3.

Method II: Classical Least Squares method

For binary mixture of PAR and MET

In order to obtain the calibration matrix K for applying CLS analysis, ten solutions of each of the pure components (PAR and MET) are prepared with concentrations in the range 30-151 and 35-175 mg/mL for PAR and MET, respectively. These ranges are previously verified to be linear relationship for each of the studied drugs. The titration volume data in the pH range of 3-12.5 (digitized every 0.1 pH) are subjected to CLS programmed in MS-EXCEL in order to obtain the calibration K matrix. The potentiometric graph of unknown mixture is then correlated with K matrix and the concentration C_{PAR} and C_{MET}, can be obtained.

For binary mixture of PAR and ASC

Similarly, ten solutions of each of the pure components (PAR and ASC) are prepared with concentrations in the

range 30-151 and 35-175 mg/mL for PAR and ASC, respectively. These ranges are previously verified to be linear relationship for each of the studied drugs in the selected solvent. The volumetric data in the pH range of 3-12.5 (digitized every 0.1 pH) are subjected to CLS programmed in MS-EXCEL in order to obtain the calibration K matrix. The potentiometric graph of unknown mixture is then correlated with K matrix and the concentration C_{PAR} and C_{ASC}, can be obtained.

Method III: Zero and First Derivative methods

For binary mixture of PAR and ASC

As demonstrated clearly in Figure 5 the concentration of ASC can be determined directly at pH 7.5 in the presence of PAR by the following equation:

$$C_{ASC} = \frac{(V_{7.5} - 0.000336)}{0.022451} \quad (20)$$

While the concentration of PAR can be determined indirectly at pH 10 knowing the volume of ASC by the following equation:

$$C_{PAR} = \frac{(V_{10} - V_{7.5} - 0.01996)}{0.01983} \quad (21)$$

On the other hand, the potentiometric graphs obtained in Method I is differentiated to obtain first order derivative graphs as shown in Figure 6. It appeared that PAR showed a substantial increase in the amplitude of dV/dpH at pH 9 where while ASC showed a substantial increase in the amplitude of dV/dpH at pH 4 without affecting each to other. Hence the pH of 9 and 4 are selected as analytical pH values for determination of PAR and ASC, respectively, without any interference from the other drugs in their combined formulation. The absolute values of D^1 (ΔpH = 11) amplitudes at pH 9 (for PAR) and the D^1 (ΔpH = 11) amplitudes at pH 4 (for ASC) are plotted against the corresponding concentrations as shown in Figure 6 and the regression parameters are given in Table 3. the concentration C_{PAR} and C_{ASC}, can be obtained as follows

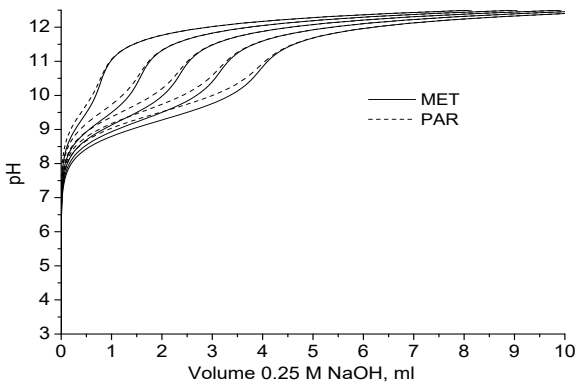
$$C_{PAR} = \frac{(V_9 - 0.0043)}{0.01142} \quad (22)$$

$$C_{ASC} = \frac{(V_4 - 0.0527)}{0.0124} \quad (23)$$

Results and discussion

PAR, MET and ASC are directly titrated potentiometrically with sodium hydroxide as the titrant. The pH titration curves of these components and their binary mixtures are shown in Figs. 3 and 4. It is obvious that the titration curves of these three analyts seriously overlap.

Figure 1 - Overlapped potentiometric curves of PAR and MET



The developed methods are validated by analysis of the synthetic binary mixtures. Table 2 and Table 4 show the known and calculated concentrated for different binary mixtures of PAR/MET and PAR/ASC.

Figure 2- Potentiometric curves and their corresponding calibration curves of PAR and MET

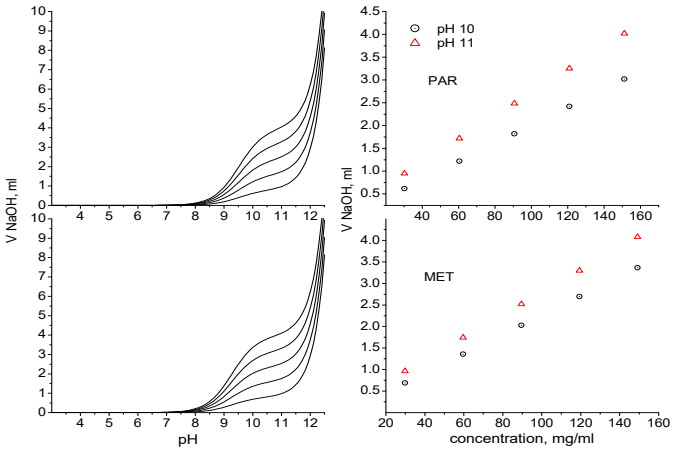


Table 1- Regression parameters for the determination of PAR and MET by simultaneous equations method

Method	pH	regression parameters					
		slope	intercept	$S_{y/x}$	r	LOD	LOQ
PAR	10	0.0672	0.0012	0.0024	0.9999	0.088	0.333
30-150 mg/ml	11	0.0265	0.0017	0.0016	0.9998	0.117	0.534
MET	10	0.2518	0.0000	0.0000	1.00	0.000	0.000
30-150 mg/ml	11	0.0994	0.0000	0.0000	1.00	0.000	0.000

* The compound used as divisor
$S_{y/x}$ = Standard deviation of residuals
LOD = Limit of detection
LOQ = Limit of quantification

Table 2 - Determination of PAR and MET in Authentic, laboratory Prepared Mixtures, using D0 and CLS

taken, mg		found, %			
		Simultaneous equations		CLS pH 3-11.5	
PAR	MET	PAR	MET	PAR	MET
30.23	29.84	99.74	100.21	100.05	99.96
30.23	89.53	99.03	100.28	100.03	99.99
30.23	149.21	101.59	99.69	99.96	100.00
90.70	29.84	99.97	100.06	99.97	100.07
90.70	89.53	100.77	99.27	100.09	99.91
90.70	149.21	100.96	99.44	99.98	100.00
151.16	29.84	100.32	98.38	99.99	100.01
151.16	89.53	100.49	99.22	100.00	99.99
151.16	149.21	101.12	98.91	99.92	100.06
Mean		100.44	99.50	100.00	100.00
S.D.		0.78	0.63	0.05	0.05

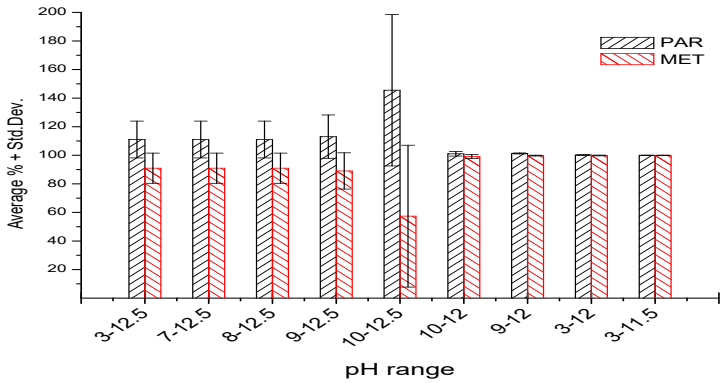


Figure 3- Recovery with error bar of PAR and MET in binary mixtures using CLS method on different pHrange

Table 3- Regression parameters for the determination of PAR and ASC by simultaneous equations method

Method		pH	regression parameters					
			Slope	intercept	$S_{y/x}$	r	LOD	LOQ
PAR 30-151 mg/ml	D_0	10	0.01984	0.019624	0.0004662	1	1.06	1.22
		7.5	0.00026	0.00048	0.000255	0.9998	4.85	11.81
	D_1	9	0.01142	0.0043	0.000876	0.9999	0.61	1.14
ASC 35-175 µg/ml	D_0	10	0.02283	0.020376	9.48E-05	1	0.90	0.93
		7.5	0.0225	0.000336	0.000203	0.9998	0.04	0.11
	D^1		4	0.0124	0.052689	0.000863	0.9998	4.46	4.94

* The compound used as divisor
$S_{y/x}$ = Standard deviation of residuals
LOD = Limit of detection
LOQ = Limit of quantification

Figure 4- Overlapped pH peaks of PAR and ASC

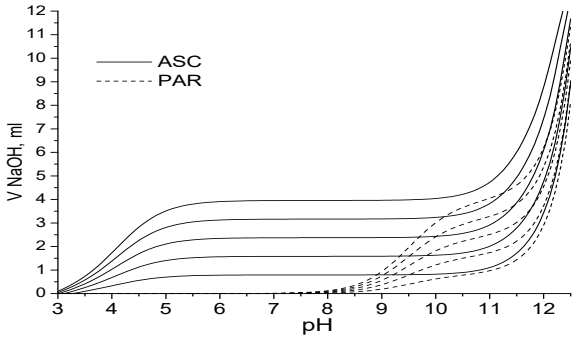
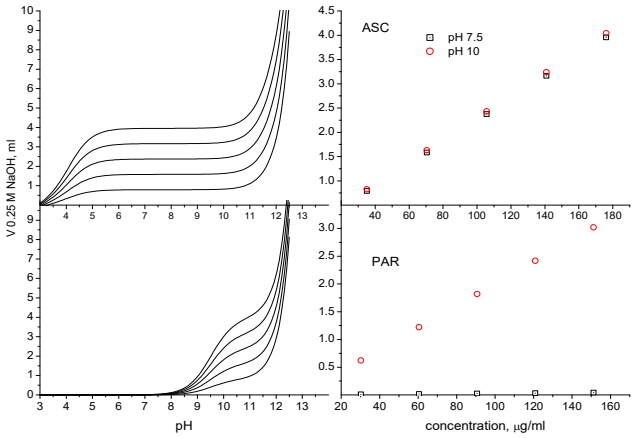


Figure 5- Potentiometric and calibration curves of PAR and ASC.



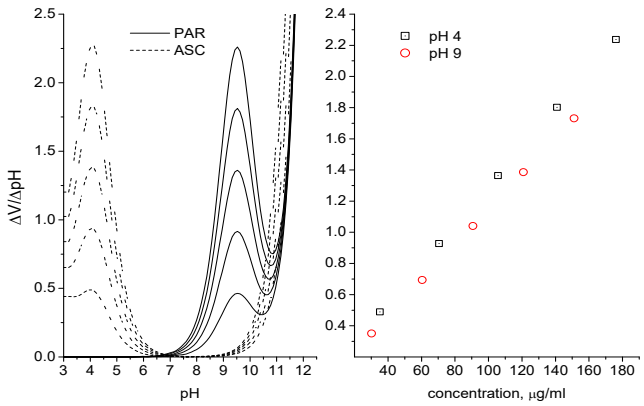


Figure 6- First derivative and its corresponding calibration curves at pH 4 for ASC and 9 for PAR

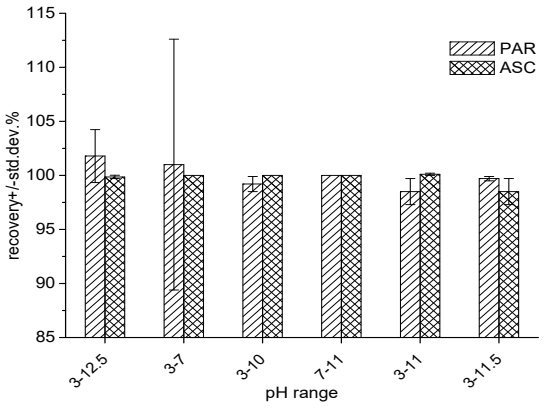


Figure 7- Recovery with error bar of PAR and ASC in binary mixtures using CLS method on different pH range

Table 4- Determination of PAR and ASC in Authentic, laboratory Prepared Mixtures, using direct, D0, D1 and CLS methods.

taken, mg		found, %							
		Direct Method		1st Derivative		Simultaneous equations		CLS (pH 7-11)	
PAR	ASC	PAR	ASC	PAR	ASC	PAR	ASC	PAR	ASC
30.23	35.22	100.88	100.96	99.65	96.31	103.32	99.99	100.00	100.00
30.23	105.67	105.36	100.33	102.01	95.66	103.30	100.00	100.00	100.00
30.23	176.12	109.84	100.21	104.04	95.39	103.29	100.01	99.99	100.00
90.70	35.22	99.40	102.92	98.63	96.22	101.07	99.99	99.99	100.03
90.70	105.67	100.85	101.00	99.36	95.58	101.02	100.03	99.98	100.00
90.70	176.12	102.35	100.60	99.99	95.49	101.03	100.02	100.00	100.00
151.16	35.22	99.11	104.96	98.41	96.37	100.63	100.06	100.01	100.05
151.16	105.67	99.97	101.65	98.76	95.64	100.59	100.02	100.00	100.01
151.16	176.12	100.87	101.00	99.26	95.42	100.60	100.02	99.98	100.00
Mean		102.07	101.51	100.01	95.79	101.65	100.02	99.99	100.01
S.D.		3.46	1.53	1.85	0.40	1.25	0.02	0.01	0.02

Application of pharmaceutical formulations

Assay results for the determination of PAR with either MET, ASC or CAF in commercial pharmaceutical are given in Table 5. RSD (%) indicates the accuracy of determination of active ingredients in the investigated pharmaceutical preparations.

It is worth to mention that CAF did not interfere on determining PAR available in Panadol Extra tablets as illustrated in (Table 5).

Table 5- Recoveries of active ingredients in pharmaceutical tablets using CLS

Content/tablet		Mean, %	RSD, %
Hepamol			
500 mg	PAR	93.48	4.81
100 mg	MET	107.67	6.77
Efferlagan			
330 mg	PAR	103.56	2.14
220 mg	ASC	93.79	2.85
Panadol Extra			
500 mg	PAR	101.46	3.12
65 mg			

Average of triplicate measurements
RSD= Relative standard deviation
PAR is determined directly in the presence of CAF in Panadol Extra tablets

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