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Short communication

Spectrophotometric determination of piroxicam and tenoxicam in pharmaceutical formulations using alizarin

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Abstract

New spectrophotometric procedures have been established for the quantitation of piroxicam and tenoxicam. The procedures are based on the reaction between the examined drug and alizarin (**I**), alizarin red S (**II**), alizarin yellow G (**III**) or quinalizarin (**IV**) producing ion-pair complexes which can be measured at the optimum wavelength. The optimization of the reaction conditions is investigated. Beer's law is obeyed in the concentration ranges 0.05–2.40 μg ml^{-1}, whereas optimum concentration as adopted from Ringbom plots was 0.12–2.25 μg ml^{-1}. The molar absorptivity, Sandell sensitivity, detection and quantification limits are also calculated. The correlation coefficient was ≥ 0.9990 ($n = 10$) with a relative standard deviation (R.S.D.) of ≤ 1.2, for ten determinations of 1.0 μg ml^{-1}. The methods are successfully applied to the determination of piroxicam and tenoxicam in their pharmaceutical formulations.

Keywords: Alizarin derivatives; Spectrophotometry; Ion pairs; Dosage forms

1. Introduction

Piroxicam (PX), 4-hydroxy-2-methyl-N-2-2-pyridinyl-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide (Fig. 1), is a non-steroidal antiinflammatory agent which is widely used in the treatment of rheumatic disease [1]. Its commercial availability for medical use is relatively recent. The properties and therapeutic efficacy of PX have been extensively described [2]. The employment of several analytical methods (ion selective electrode voltammetry, spectrofluorometry, chromatography, spectrophotometry) for the determination of PX in pharmaceutical samples and biological fluids has been proposed [3–10].

Tenoxicam TX, [4-hydroxy-2, methyl-N-pyridyl-2H-thieno (2,3-e)-1,2-thiazine-3-carbxamide-1,1-dioxide], is a new non-steroidal drug which has antiinflammatory, analgetic and antipyretic effects. The drug is widely used in the treatment of rheumatic diseases [11,12]. It is a derivative of oxicam with a thiophene ring replacing the benzene ring in piroxicam. Tenoxicam inhibits cyclooxygenase which catalyses the formation of cyclic endoperoxides [13,14]. Liquid chromatography (LC) is predominantly used for the determination of the drug in biological fluids. Dixon et al. [15] reported LC method for the

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determination of tenoxicam in plasma with detection limit of 0.1 μg ml^{-1}. A very recent LC was applied to estimate the drug in plasma [16] and in urine samples [17] using piroxicam as an internal marker. Stability of tenoxicam in stearate and lipophilic semi-solid system gel system suitable for topical 'soft-patch' formulations were investigated by HPLC [18]. The electrochemical behavior of TX has been investigated [19–22]. Recently, some spectrophotometric methods were used for its determination [23–26].

The goal of the present work is to develop spectrophotometric methods that can be used in laboratories where modern and expensive apparatus such as GLC and HPLC are not available. Moreover, the developed methods are more simple, rapid, accurate, precise and sensitive for the determination of PX and TX and to apply the procedures to various dosage forms. The method is based on ion pair complex formation between the drug and alizarin derivatives under investigation.

2. Experimental

2.1. Apparatus

A JASCO 530 V spectrophotometer with a 10 mm quartz cell was used for all spectrophotometric measurements and an Orion research model 601 A/digital ionalyzer was used for checking the pH of phosphate buffer solutions of pH values 2.0–12.0 prepared by the recommended method [27].

2.2. Reagents

Alizarin, 1,2-dihydroxyanthraquinone (**I**), alizarin red S, 3,4-dihydroxy-9,10-dioxo-2-anthracene sulfonic acid (**II**), alizarin yellow G, 5-(4-nitrophenylazo)salicylic acid (**III**) and quinalizarin, 1,2,5,8-tetrahydroxyanthraquinone (**IV**) were Aldrich products and used without further purification. A stock solution (2×10^{-3} M) was prepared by dissolving the appropriate weights of **II** and **III** in doubly distilled water, while that for **I** and **IV** was dissolved in acetone.

Pfizer Egypt Company, Cairo, Egypt, supplied Piroxicam and its dosage forms (i.e. feldene tablets, feldene capsules and feldene suppositories). Egyptian International Pharmaceutical Industrial Company, Egypt supplied Tenoxicam and its pharmaceutical formulations (i.e. Epicotil tablets and Epicotil suppositories).

Standard stock solution of piroxicam and tenoxicam, 100 μg ml^{-1}, were prepared by dissolving 25 mg of the drug in 250 ml acetone. 2×10^{-3} M PX and TX solutions were prepared by dissolving an appropriate weight in 100 ml acetone in the same manner.

2.3. General procedures

An aliquot containing from 0.5 to 24 μg of PX or TX were transferred into a 10 ml calibrated flask. 1.0 ml of 2×10^{-3} M of reagent **IV** for both drugs and **I** for TX, 3.0 ml 2×10^{-3} M of reagent **II** for both drug and **I** for PX, and 0.2 ml of **III** for both drugs was added to each flask. Four milliliters of the optimum buffer media of the optimum pH value for each system as recorded in Table 1 was added and 2.0 ml of acetone was added to achieve 30% (v/v) in the final assay solution. For each system, the optimum time and temperature as recorded in Table 1 is attained and completed each flask to 10 ml with water. The absorbance was measured for each system at the optimum wavelength (Table 1) against a reagent blank prepared in the same way without addition of the examined drug.

2.4. Application to various dosage forms

2.4.1. Tablets and capsules

The contents of 20 capsules, or finely ground

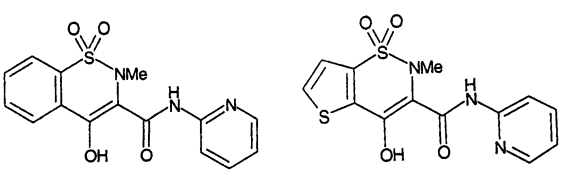

Fig. 1. Piroxicam and tenoxicam.

Table 1
Quantitative parameters for the complexation of PX and TX with alizarin derivatives (**I**–**IV**)

Parameter	Piroxicam							
	I	**II**	**III**	**IV**	**I**	**II**	**III**	**IV**
pH	7.5	6.5	8.2	7.5	6.5	7.5	7.0	8.2
λ_{max}	538	529	355	579	546	531	370	579
Reagent (10^{-4})	6.0	6.0	0.4	2.0	2.0	6.0	0.4	2.0
Acetone ratio (%)	30	30	30	30	30	30	30	30
Time (min)	5.0	2.0	2.0	2.0	5.0	2.0	2.0	5.0
Temperature (°C)	60	25	25	25	60	25	25	25
Stability (h)	24	24	30	24	28	30	36	30
Beer's limits (μg ml^{-1})	0.05–1.50	0.05–1.90	0.05–2.20	0.05–2.40	0.05–1.60	0.05–1.40	0.05–2.20	0.05–2.40
Ringbom concentration (μg ml^{-1})	0.10–1.40	0.12–1.75	0.10–2.10	0.12-2.25	0.12–1.45	0.12–1.25	0.15–2.00	0.12–2.25
Molar absorptivity (l mol^{-1} cm^{-1})	3.95×10^5	2.01×10^5	4.02×10^5	1.82×10^5	8.77×10^4	2.85×10^5	3.05×10^5	1.70×10^5
Sandell sensitivity (ng cm^{-2})	0.81	1.58	0.79	1.75	3.64	1.12	1.05	1.88
Detection limit (ng ml^{-1})	13	14	12	12	12	14	15	16
Quantification limit (ng ml^{-1})	45	47	40	43	40	45	48	50
Regression equation[a]								
Slope	0.81	0.63	1.26	0.57	0.28	0.89	0.95	0.53
Intercept	−0.007	0.011	0.009	−0.003	0.01	−0.005	−0.008	0.006
R.S.D. of slope	0.0018	0.0026	0.0013	0.0017	0.0022	0.0025	0.0011	0.0020
R.S.D. of intercept	0.0029	0.0032	0.0018	0.0023	0.0030	0.0031	0.0019	0.0028
Correlation coefficient (r)	0.9992	0.9990	0.9994	0.9996	0.9990	0.9996	0.9995	0.9991
R.S.D. (%)[b]	0.90	1.00	1.20	0.80	1.10	1.20	1.00	1.10
Range of error (%)	0.75	0.90	1.30	1.29	1.00	1.10	0.80	0.75

[a] $A = a + bC$ (where C is the concentration of drug in μg ml^{-1}).
[b] Average of ten determinations.

tablets were weighed and mixed. An amount of the tablet powder, or capsule powder equivalent to 250 mg of PX or TX was weighed, dissolved in acetone and any remaining residue was removed by filtration. The clear solution was diluted to 250 ml with acetone in a 250 ml calibrated flask. The

drug content of this solution was obtained by applying the general procedure to aliquot containing 1.0 μg ml^{-1} of the drug as described above

2.4.2. Suppositories

At least ten suppositories were weighed, cut into small pieces and transferred to a small porcelain dish. They were melted by stirring in a water bath to homogenize and cooled; then weighed portions equivalent to 25 mg PX, or TX were transferred into a beaker, melted and dissolved in acetone, by stirring using a magnetic stirrer at 60 ± 1.0 °C. The solution was cooled, filtered, diluted to 250 ml with acetone in a 250 ml calibrated flask and analyzed as described above under the general procedure.

2.5. Stoichiometric relationship

Job's method of continuous variation was employed; a 2×10^{-3} M standard solution of PX or TX and 2×10^{-3} M solution of reagents (**I**–**IV**) were used. A series of solutions were prepared in which the total volume of drug and reagent was kept at 2.0 ml. The reagents were mixed in various proportions and diluted to volume in a 10 ml calibrated flask with the appropriate solvent following the above mentioned procedure.

3. Results and Discussion

3.1. Absorption spectra

The absorption spectra of PX or TX and their complexes with alizarin derivatives (**I**–**IV**) under the optimum conditions are shown in Fig. 2. The absorption band of the reagent showed λ_{max} at 442, 445, 336 and 491 nm, whereas that of PX complexes are located at 538, 529, 355 and 579 nm and TX complexes at 546, 531, 370 and 579 nm, respectively, where the reagent gives almost zero absorbance. However, in all instances, the absorbance was measured at those λ_{max} against a reagent blank prepared under identical conditions.

Investigations were carried out to establish the most favorable conditions to give a highly intense color and to achieve maximum color development in the quantitative determination of the examined drugs. The influence of each of the following variables on the reaction was tested.

3.1.1. Effect of pH

The effect of pH on the drug reagent system was studied over the pH range 2.0–12 using different types of buffer solutions (acetate, borate, universal, phosphate and thiel buffers [27]). Phosphate buffer solution is used to maintain the optimum one to give highest absorbance value in addition to the stability of the color without affecting the absorbance in the pH range 6.5–8.5. For PX complexes, the pH 7.5, 6.5, 8.2 and 7.5 were used for **I**, **II**, **III** and **IV**, respectively, whereas for TX complexes, the optimum pH values were 6.5, 7.5, 7.0 and 8.2, respectively. Moreover, the optimum volume of buffer solution added to 10 ml to give constant absorbance value was also studied and found to be 4.0 ml.

3.1.2. Effect of reagent concentrations

When the general procedure was followed with varied amounts of 2×10^{-3} M reagent solution, maximum and constant absorbance was obtained with 1.0 ml for PX complex with reagent **IV** and TX with **I** and **IV**. For PX complexes with **I** and **II** or TX with **II**, 3.0 ml 2×10^{-3} M reagent gave the highest absorbance values. For reagent **III**

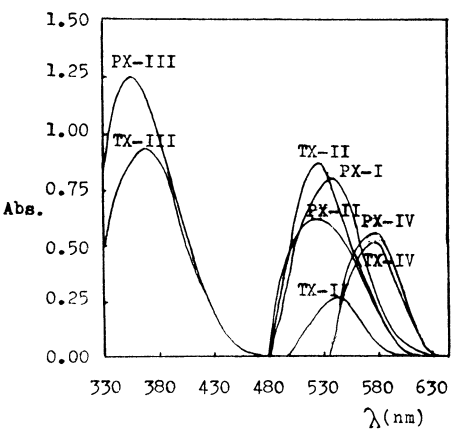

Fig. 2. Absorption spectra of the ion pairs of 1.0 μg ml^{-1} of PX or TX complexed with reagents (**I**–**IV**) against reagent as blank.

complexes with PX and TX, 0.2 ml only gave the highest and constant absorbance.

3.1.3. Effect of solvent

The solvents studied were methanol, ethanol, propanol, acetone, dioxane and dimethylformamide. Methanol and acetone gave the maximum color intensity but acetone stabilized the formed complex for a longer time. The maximum and stable absorbance value is obtained with 30% acetone (v/v). A higher level of acetone than 40% caused a decrease of absorbance value.

3.1.4. Effect of time and temperature

The optimum reaction time was determined by following the color development at ambient temperature (25 ± 2 °C). Complete color development was attained after 2.0 min for PX with reagents **II**, **III** and **IV** and also for TX with reagent **II** and **III**, whereas for TX with reagent **IV** maximum color intensity was attained after 5.0 min. Other complexes take from 60 to 75 min for completion. To minimize the reaction time, the reaction mixture was heated in a water bath of different temperature at different time. Complete color development was obtained after heating for 5.0 min at 60 ± 1 °C for PX and TX with reagent **I**. The absorbance remains constant for at least 24 h.

3.1.5. Sequence of additions

The most favorable sequence is 'drug–reagent–buffer–acetone' for the highest absorbance and stability. Other sequences needed longer time in addition to lower stability. The complexes with this sequence remain stable for at least 24 h.

3.2. Stoichiometric ratio

The molar ratio of drug to reagent (**I**–**IV**) in the complex was determined by Job's method of continuous variations, which was found to be 1:1. The conditional stability constants (log K), calculated with Harvey and Manning equation [28] applying the data obtained from the continuous variation method, was calculated and recorded in Table 1.

3.3. Effect of interferences

To assess the usefulness of the method, the effect of additives, diluents and excipients that often accompany PX and TX in their dosage forms (lactose, glucose, saccarose, glycerol, magnesium streate, propylene glycol and starch) was studied. The results indicated that up to 150 fold excess of them do not interfere (absorbance change by $\pm 3.0\%$ is non-interference). Also there is no interference from the degradate product resulted from thermal or hydrolytic degradation, indicating a high selectivity for determining PX or TX in their pharmaceutical formulations, in addition to a high stability indicating assay.

3.4. Analytical data

Under the optimum experimental conditions, there was a linear relationship between absorbance and drug concentration in the range 0.05–2.4 μg ml^{-1} with a correlation coefficient (r) ≤ 0.9990 (Table 1). For more accurate analysis Ringbom optimum concentration range was calculated and recorded in Table 1. The regression equation, the apparent molar absorptivity and Sandell sensitivity were also calculated from the calibration graph applying least square method (Table 1).

The reproducibility of the proposed methods was determined by running ten replicate samples, each containing 1.0 μg ml^{-1} of PX or TX in the final assay solution. At this concentration, the relative standard deviations (R.S.D.) are calculated and recorded in Table 1.

The relative sensitivities of the four reagents can be determined by comparing the molar absorptivities of the chromogens (Table 1). Reagent **III** exhibited the most intense bands and were, therefore, selected for all further study.

In order to determine the accuracy and precision of the proposed methods, solutions containing four different concentrations of PX and TX were prepared and analyzed in quintuplicate. The measured standard deviations (S.D.) (s), R.S.D. (S_r), the standard analytical errors and confidence limits (Table 2) can be considered satisfactory, at least for the levels of concentrations examined.

Table 2
Evaluation of accuracy and precision of the proposed method

Ion pair	Taken (μg ml^{-1})	Found (μg ml^{-1})[a]				S.E.	Confidence limits
		O	*P*	*S*	S_r (%)		
I-PX	0.3	0.305	0.298	0.05	0.67	0.020	0.298 ± 0.060
	0.6	0.611	0.604	0.07	0.83	0.029	0.604 ± 0.080
	0.9	0.885	0.905	0.04	0.55	0.016	0.905 ± 0.050
	1.2	1.225	1.192	0.03	0.49	0.012	1.192 ± 0.035
I-TX	0.4	0.394	0.4034	0.08	1.11	0.033	0.4034 ± 0.095
	0.8	0.790	0.805	0.06	0.90	0.024	0.805 ± 0.070
	1.2	1.185	1.196	0.09	1.35	0.037	1.196 ± 0.110
	1.6	1.580	1.610	0.05	0.76	0.020	1.610 ± 0.060
II-PX	0.2	0.203	0.201	0.07	1.05	0.029	0.201 ± 0.080
	0.7	0.712	0.695	0.06	0.88	0.024	0.695 ± 0.070
	1.2	1.220	1.208	0.09	1.36	0.037	1.208 ± 0.110
	1.7	1.678	1.710	0.04	0.63	0.016	1.710 ± 0.050
II-TX	0.1	0.097	0.101	0.06	0.91	0.024	0.101 ± 0.070
	0.5	0.505	0.497	0.10	1.45	0.41	0.497 ± 0.120
	0.9	0.914	0.894	0.09	1.27	0.037	0.894 ± 0.110
	1.3	1.320	1.310	0.07	1.08	0.029	1.310 ± 0.080
III-PX	0.5	0.493	0.504	0.04	0.65	0.016	0.504 ± 0.050
	1.0	0.990	1.007	0.08	1.20	0.033	1.007 ± 0.095
	1.5	1.515	1.495	0.03	0.52	0.012	1.495 ± 0.035
	2.0	2.020	1.991	0.05	0.74	0.020	1.991 ± 0.050
III-TX	0.6	0.607	0.595	0.03	0.56	0.012	0.595 ± 0.035
	1.1	1.111	1.104	0.06	0.80	0.024	1.104 ± 0.070
	1.6	1.585	1.610	0.07	0.98	0.029	1.610 ± 0.080
	2.1	2.080	2.112	0.04	0.58	0.016	2.112 ± 0.050
IV-PX	0.3	0.296	0.302	0.09	1.29	0.037	0.302 ± 0.110
	0.9	0.908	0.897	0.12	1.60	0.050	0.897 ± 0.140
	1.5	1.515	1.494	0.10	1.45	0.041	1.494 ± 0.120
	2.2	1.225	2.210	0.08	1.33	0.033	2.210 ± 0.095
IV-TX	0.2	0.203	0.199	0.08	1.10	0.033	0.199 ± 0.095
	0.9	0.890	0.905	0.10	1.44	0.041	0.905 ± 0.012
	1.6	1.583	1.591	0.07	1.00	0.029	1.591 ± 0.080
	2.4	2.425	2.390	0.09	1.18	0.037	2.390 ± 0.110

[a] Average of six determinations.

The S.D. of the absorbance measurement was 0.0032 obtained from a series of 13 blank solution. The limits of detection ($K = 3$) and of determination ($K = 10$) of the method were established according to the IUPAC definitions ($C_1 = KS_o/s$ where C_1 is the limit of detection, S_o is the standard error of blank determination, s is the slope of the standard curve and K is the constant related to the confidence interval) [29]. The calculated values were recorded in Table 1 for all drug-reagent CT complexes. The R.S.D. were obtained from a series of 10 standards each containing 1.0 μg ml^{-1} of drug and the results are recorded in Table 1.

3.5. Analytical applications

The proposed procedures were successfully applied to various dosage forms, viz. tablets, capsules and suppositories. The results are recorded in Table 3, and compared statistically with the official methods [30]. For further confirmation, the standard addition method was applied to test the reliability and recovery of the proposed proce-

Table 3
Determination of PX and TX in pharmaceutical formulations applying the standard addition technique

Pharmaceutical formulations	Content (mg)	Taken (μg ml^{-1})	Added (μg ml^{-1})	Found (μg ml^{-1})[b]				
				I	**II**	**III**	**IV**	Off.
Capsules								
Feldene	10 mg PX	0.50	-	0.495	0.503	0.502	0.497	0.490
			0.50	1.004	0.999	1.005	0.998	0.984
			1.0	1.494	1.508	1.497	1.505	1.480
			1.50	–	–	1.992	2.010	1.974
t-value[a]				1.40	1.06	1.28	1.54	
F-test[a]				2.76	2.30	2.61	3.17	
Feldene	20 mg PX	0.35	–	0.351	0.350	0.348	0.352	0.355
			0.70	1.054	1.047	1.045	1.055	1.040
			1.00	1.355	1.344	1.360	1.342	1.335
			1.30	–	1.656	1.645	1.640	1.665
t-value[a]				1.33	1.56	1.12	1.45	
F-test[a]				2.48	3.04	2.40	2.88	
Tablets								
Feldene	10 mg PX	0.70	–	0.703	0.698	0.705	0.704	0.691
			0.50	1.205	1.208	1.195	1.193	1.184
			1.00	–	1.694	1.710	1.692	1.720
			1.50	–	–	2.194	2.210	1.175
t-Value[a]				1.59	1.09	1.41	1.27	
F-test[a]				3.15	2.23	2.72	2.63	
Epicotil	20 mg TX	0.40	-	0.398	0.401	0.402	0.403	0.409
			0.40	0.805	0.797	0.804	0.795	0.815
			0.80	1.206	1.203	1.195	1.193	1.220
			1.20	1.595	–	1.606	1.610	1.635
t-Value[a]				1.37	1.15	1.63	1.25	
F-test[a]				2.76	2.50	3.41	2.66	
Suppositories								
Feldene	20 mg PX	0.60	–	0.603	0.598	0.597	0.604	0.592
			0.35	0.945	0.956	0.960	0.942	0.935
			0.70	1.310	1.293	1.290	1.308	1.270
			1.10	–	1.707	1.710	1.690	1.665
t-Value[a]				1.56	1.17	1.48	1.05	
F-test[a]				3.23	2.64	2.92	2.31	
Epicotil	20 mg TX	0.45	-	0.448	0.451	0.450	0.453	0.444
			0.45	0.905	0.903	0.898	0.879	0.910
			0.90	1.344	1.355	1.360	1.353	1.365
			1.35	–	–	1.790	1.808	1.820
t-Value[a]				1.32	1.09	1.62	1.18	
F-test[a]				2.87	2.46	3.12	2.67	

[a] Theoretical *t*-and *F*-values for 5° of freedom and at 95% confidence level are 2.57 and 5.05, respectively.
[b] Average of six determinations.

dures, since the ion-pair complexes are stable for at least 24 h. The recovery studies were carried out after adding known quantities of pure drug to the preanalyzed formulations. The percentage recoveries were found to be close to 100% (Table 3). The high percentage recoveries indicate no interferences from ingredients and excepients that might be found in different formulations. Consequently, the methods are simple, rapid and stability indicating assay.

The results obtained from the proposed procedures were compared with those obtained using the official method [30]. The accuracy via *t*-value and the assessment of precision via *F*-test for 5° of freedom and 95% confidence level were calculated and the results indicated that there is no significance difference between them (Table 3). Moreover, the proposed methods are more stable (at least for 24 h) than the official method [30].

4. Conclusion

It is clear that alizarin derivatives (**I**–**IV**) are highly sensitive reagents for the determination of PX and TX compared with other reagents [8,23–25]. Although the methods using other reagents [7,26] are more sensitive compared with the proposed procedures, the latter is more time consuming (maximum time is 5.0 min), in addition to high stability and tolerance limits for additive and excepients. Although the color development of reagent **I**-PX and **I**-TX ion pairs at room temperature requires from 60 to 75 min for completion, this can be shortened to 5.0 min by raising the temperature to 60 °C. The relative sensitivities of the four reagents can be determined by comparing the molar absorptivities of the chromogens (Table 1). Reagent **III** exhibited the most intense bands and were, therefore, selected for all further study.

The present procedures used a relatively small amount of drug, and are simple, direct, fast, accurate and applicable over a convenient range of concentrations of PX and TX. Therefore, these procedures can be recommended for routine quality control analysis of PX and TX. The procedures are considered as a stability-indicating assay since there are no interferences from other ingredients.

References

[1] H.H. Chang, S.H. Dromgoole, in: H.E. Paulus, S.H. Dromgoole (Eds.), Drugs for Rheumatic Disease, Churchill Livingstone, New York, USA, 1987, p. 18.
[2] R.N. Brogden, R.C. Heel, T.M. Speight, G.S. Avery, Drugs 22 (1981) 165.
[3] M.A. Al-Ries, Anal. Lett. 31 (1998) 793.
[4] J.A. Acuna, C. Delafuente, M.D. Vazquez, M.L. Tascon, Talanta 40 (1993) 1637.
[5] E. Hackmann, E. Gianotto, M.I. Santoro, Anal. Lett. 26 (1993) 259.
[6] S.A. Avgerinos, J. Dragatsis, T.H. Kaiidas, S. Malamataris, J. Chromatogr. B 673 (1995) 142.
[7] G.M. Escandar, Analyst 124 (1999) 587.
[8] J. Parasrampuria, V.D. Gupta, Drug Dev. 16 (1992) 629.
[9] V. Rodenad, G.M. Soledad, P.C. Sanchez, M.I. Albero, Analyst 123 (1998) 1749.
[10] S. Kahalil, N. Borham, M.A. El-Ries, Anal. Chim. Acta 414 (2000) 215.
[11] J.F. Gonzales, P.A. Todd, Drugs 341 (1987) 298.
[12] The Merck Index, 11th ed., Merck Rahway, NJ, USA, 1989, p. 1441.
[13] T.F. Woolf, L.L. Radulovic, Drug Metab. Rev. 21 (1989) 255.
[14] P. Heizmann, J. Korner, K. Kinapold, J. Chromatogr. Biomed. Applic. 374 (1986) 95.
[15] J.S. Dixon, J.R. Lowe, D.B. Galloway, J. Chromatogr. 310 (1984) 455.
[16] M.I.M. Jaramillo, S.B. Garces, J. Chromatogr. 349 (1993) 616.
[17] D. Dell, R. Joly, W. Meiester, W. Arnold, C. Patros, B. Guldimanm, J. Chromatogr. 317 (1984) 483.
[18] G. Csoka, S. Morton, R. Zelko, I. Raez, STP Pharm. Sci. 10 (2000) 415.
[19] Z. Atkopur, M. Tuncell, Anal. Lett. 29 (1996) 2383.
[20] N. Ozaltin, Anal. Chim. Acta 406 (2000) 183.
[21] N. Abo El-Maali, J.C. Vire, G.J. Patriarche, M.A. Ghandour, G.D. Christian, Anal. Sci. 6 (1990) 245.
[22] N. Ozaltin, Anal. Chim. Acta 406 (2000) 183.
[23] G. Yener, Y. Topaaloglu, Sci. Pharm. 60 (1992) 247.
[24] O. Atay, E. Dincol, Anal. Lett. 30 (1997) 1675.
[25] S.A. Al-Tamrah, Anal. Chim. Acta 375 (1998) 277.
[26] M.S. Carcia, C. Sanchez-Pedreno, M.I. Gimenez, J. Pharm. Biomed. Anal. 21 (1999) 731.
[27] H.T.S. Britton, Hydrogen Ions, fourth ed., Chapman & Hall, 1952.
[28] A.E. Harvey, D.L. Manning, J. Am. Chem. Soc. 71 (1950) 4488.
[29] IUPAC Compendium of Analytical Nomenclature Definitive Rules. H.M.N.H. Irving, H. Freiser, T.S. West (Eds.), Pergamon Press, Oxford, 1981.
[30] United States Pharmacopeia, 24th Review, The National Formulary, 19th Review, The United States Pharmacopeial convention, Rockville, MD, 2000.