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Il Farmaco 56 (2001) 579–585

IL FARMACO

Application of potassium dichromate and iron–thiocyanate in the spectrophotometric investigations of phenothiazines☆

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Received 14 September 2000; accepted 26 January 2001

Abstract

A spectrophotometric procedure for the determination of phenothiazines in pure form and in a number of their pharmaceutical preparations has been developed that offers the advantages of simplicity, accuracy, precision and sensitivity over many other methods. The method is based on the oxidation of phenothiazines by a known excess amount of potassium dichromate followed by the estimation of unreacted amount of dichromate by reacting with excess of iron(II) and measuring the iron(III) formed by complexing with thiocyanate. The reacted oxidant corresponds to the drug content. Different variables affecting the reaction between drugs and dichromate were studied and optimized. At the maximum absorption of 480 nm, Beer's law is obeyed in the range 2.5–29.75 μg/ml. The molar absorptivity and Sandell sensitivity of the procedure were calculated in addition to detection limit. Statistical treatment of the experimental results indicates that the procedure is precise and accurate. Excipients used as additives in pharmaceutical formulations did not interfere in the proposed procedure. The reliability of the method was established by parallel determination against the official BP methods. The procedure described was successfully applied to the determination of the bulk drugs and in pharmaceutical formulations.

Keywords: Phenothiazines determination; Spectrophotometry; Potassium dichromate; Iron(III)–thiocyanate complex

1. Introduction

Phenothiazines are a group of drugs that are widely used as tranquillizers antihistamines and hypnotics. They also possess analgesic and antipyretic properties. The increasing use of these drugs in medicine has prompted the development of several methods for their determination in pure form and in pharmaceutical preparations and these methods have been reviewed by several workers [1,2]. The assay procedure listed in British Pharmacopoeia (BP) for phenothiazines describes non-aqueous titrimetric methods for determination of drugs in pure form and UV-spectrophotometric methods for preparations [3]. Methods involving UV spectroscopy [4,5], HPLC [6,7], GC [8], spectrofluorometry [9,10] and voltammetry [11,12] have been applied for the determination of these compounds. Several studies have been proposed for visible spectrophotometric determination of phenothiazines based on radical cation formation [13–16], diazotization and coupling reaction [17], oxidative coupling reaction [18], charge-transfer complex formation [19] and ion-association complex formation [20].

Phenothiazine drugs have also been assayed by indirect spectrophotometric methods involving vanadium(V) [21] and chromium(VI)–s-diphenylcarbazide [22] and chromium (VI)–metol [23] systems.

In recent years, combination of iron–1,10-phenanthroline system has been utilized for the indirect spectrophotometric determination of several pharmaceuticals [24–28]. To the best of our knoweldge, however, there is no work in the literature reported about the application of iron–thiocyanate system for the determination of pharmaceuticals.

The present work aims to demonstrate a simple and sensitive method suitable and convenient for the determination of six phenothiazines using potassium dichromate as an oxidant and iron–thiocyanate system for measuring the unreacted dichromate.

☆ This work was presented at the National Conference on 'Recent Trends in Structure, Functions, Analysis of Molecules and Applications' held at Mysore, India, 28–30 October, 1999.

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0014-827X/01/$ - see front matter
PII: S0014-827X(01)01096-5

2. Results and discussion

Attempts to oxidize phenothiazine drugs with a known excess of iron(III) and to subsequently determine unreacted iron(III) with thiocyanate in hydrochloric acid medium as a step to the indirect determination of phenothiazines were unsuccessful since iron(III) was found to be a poor oxidizing agent for these drugs. Hence, we used a combination of dichromate and iron(III)–thiocyanate system for the determination of phenothiazines. Complex formation between iron(III) and thiocyanate is a well-known reaction that has been extensively used for the trace level determination of iron [30].

The proposed method is based on the oxidation of phenothiazine drugs by a known excess of dichromate in hydrochloric acid medium, reducing the unreacted dichromate with iron(II) and subsequent formation of iron(III)–thiocyanate complex, before measuring the absorbance of the latter at 480 nm. Phenothiazine drugs when added in increasing amounts, consume dichromate and are oxidized to respective sulphoxides [16]. Consequently, there is a concomitant fall in the dichromate concentration. When the unreacted dichromate is reduced by a fixed amount of iron(II), there will be a concomitant decrease in the concentration of iron(III) formed. This is observed as a proportional decrease in the absorbance of iron(III)–thiocyanate complex on increasing the concentration of phenothiazine drugs (Fig. 1). The absorbance is found to decrease linearly with increasing concentration of phenothiazines which forms the basis for their determination. The reaction scheme is presented in Fig. 2.

Two blanks were prepared for this study. The reagent blank which contained optimum concentrations of all the reagents except drug gave maximum absorbance (Fig. 1). The other blank was prepared in the absence of the oxidizing agent ($K_2Cr_2O_7$) and the drug to determine the contribution of other reagents to the absorbance of the system. Since the absorbance of the second blank was negligible, the absorbance of the developed color was measured against distilled water. Chromium(III) produced in the reaction is so small (max. concentration is ~ 1 μg/ml) that it does not interfere in the measurement at 480 nm.

2.1. Optimization of reaction conditions

The conditions for the determination of iron(III) with thiocyanate are well established [30]. Hence, the various parameters involved in the oxidation of the drugs by dichromate and subsequent reduction of unreacted dichromate by iron(II) were optimized. Though nitric or hydrohloric acid medium could be used for the complexation of iron(III) with thiocyanate, hydrochloric acid was selected because, this was the ideal choice since nitric acid, being an oxidizing agent, interferes with the oxidation of drugs by dichromate. Sulphuric acid medium, though convenient for the oxidation of drugs by dichromate, was not preferred since it reduces the color intensity of iron(III)–thiocyanate complex [30]. A 1 M hydrochloric acid was found adequate for the oxidation of the drugs by dichromate as well as the complex formation of iron(III) with thiocyanate.

Because of non-linearity at higher concentrations [30], 6 μg/ml was taken as the upper limit of determina-

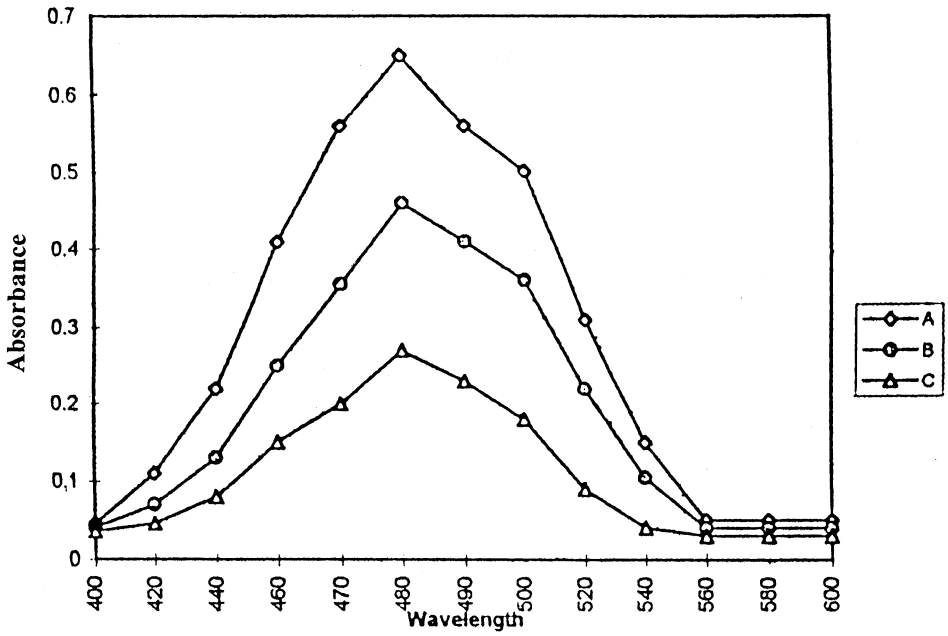

Fig. 1. Absorption spectra measured against distilled water. (A) Blank; (B) 50 μg of PH; and (C) 100 μg of PH.

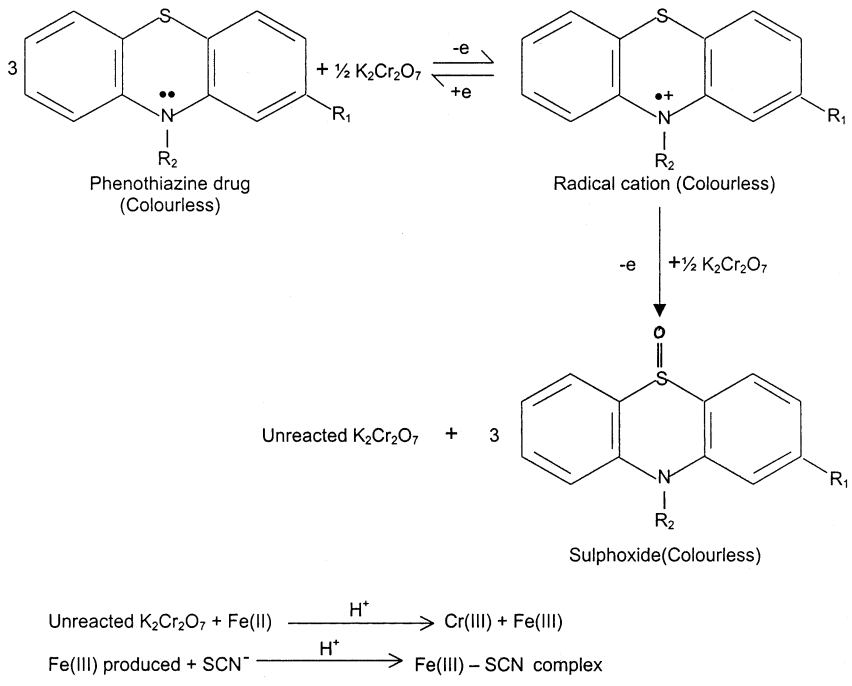

Fig. 2. Reaction scheme showing the formation of iron(III)–thicyanate complex and correlation of latter's concentration to phenothiazine drug concentration.

Table 1
Analytical parameters and optical characteristics of the proposed method

Parameter	CPH	PH	TPH	TFPH	FPH	PCPMS
Reaction time (min)	25	25	25	20	30	30
Stability period (min)	45	45	120	90	60	60
Beer's law limits (μg/ml)	2.5–17.5	2.5–15.0	2.5–17.5	2.5–24.0	2.5–25.0	4.0–30.0
Detection limit (μg/ml)	0.1570	0.0893	0.0864	0.1304	0.0833	0.1385
Molar absorptivity (l mol^{-1} cm^{-1})	1.30×10^4	1.20×10^4	1.26×10^4	1.26×10^4	1.24×10^4	1.34×10^4
Sandell sensitivity (ng cm^{-2})	2.7	2.6	3.1	3.8	4.1	5.1
Regression equation [a]						
Intercept (a)	0.6455	0.6457	0.6473	0.6436	0.6449	0.6408
Slope (b)	−0.0359	−0.0379	−0.0330	−0.0267	−0.0255	−0.0187
Correlation coefficient (r)	−0.9996	−0.9996	−0.9995	−0.9996	−0.9993	−0.9991

[a] $Y = a + bX$, where 'Y' is the absorbance for concentration 'X' in μg/ml.

tion of iron(III). Stoichiometrically, 44.77 μg of potassium dichromate would be required to generate it from 314 μg of ammonium ferrous sulphate. However, slightly large amounts (50 μg of $K_2Cr_2O_7$ and 400 μg of ammonium ferrous sulphate) were used to ensure quantitative reaction. Though a fixed amount of ammonium ferrous sulphate is not really needed, large amounts are undesirable since iron(II) tends to undergo aerial oxidation. Hence, a fixed amount (400 μg) of ammonium ferrous sulphate, enough to reduce the total $K_2Cr_2O_7$ used, was employed in the investigation.

The oxidation of the drugs by dichromate was complete in 20–30 min depending on the individual phenothiazine drug (Table 1) but subsequent oxidation of iron(II) to iron(III) and complexation of the latter with thiocyanate were instantaneous under the experimental conditions described. The developed color was stable for 45–120 min (Table 1).

2.2. Analytical data

The reaction times, the stability periods, Beer's law limits, detection limits [31], molar absorptivities and Sandell sensitivities are given in Table 1. The slopes, intercepts and correlation coefficients obtained by linear least squares treatment are also given in Table 1. Since the absorbance of the iron(III)–thiocyanate system is measured ultimately, within the experimental error, nearly constant values for intercept and molar absorptivity were obtained for different phenothiazines

indicating that the reaction between dichromate and the drugs is stoichiometric and quantitative. Further, though the literature value of molar asbsorptivity for iron(III)–thiocyanate complex is 7×10^3 l mol^{-1} cm^{-1} [32], slightly higher values ($\sim 1.2 \times 10^4$ l mol^{-1} cm^{-1}) were obtained in this study since the values refer to the phenothiazine drugs.

The precision of the method was tested by analysing six replicate samples of CPH or TPH (120 μg), PH (100 μg), TFPH or FPH (160 μg) and PCPMS (300 μg). The amount found, percent error, relative standard deviation and percentage range of error obtained for each drug are presented in Table 2, and indicate high accuracy and precision of the method.

2.3. Interferences

In pharmaceutical analysis, it is important to test the selectivity toward the excipients and the fillers added to the pharmaceutical preparations. Commonly encountered excipients such as starch, talc, glucose, alginate and stearate did not interfere. This is clear from the results obtained for the pharmaceutical formulations (Table 3).

2.4. Application to dosage forms

The method was applied to the determination of studied drugs in their pharmaceutical dosage forms (Table 3). The performance of the proposed method was assessed by calculation of *t*- and *F*-values compared with the official methods [3]. At 95% confidence level, the calculated *t*- and *F*-values did not exceed the tabulated values, indicating that the proposed and official methods are equally accurate and precise. The results demonstrate the suitability of the proposed method for the routine analysis of pharmaceutical preparations containing the studied drugs.

The proposed method, besides being simple, accurate and precise, is free from many disadvantages that are common with the direct spectrophotometric methods. For example, the method of Issa et al. [33] is poorly sensitive and the entire procedure is carried out in ethanolic solution. The reaction with 2-iodobenzoate [34] requires high H_2SO_4 concentration while some procedures [35,36] involve heating the reaction mixture in boiling water bath for several min. The method proposed by Dembinski [37] based on the use of Reinecke salt requires precipitation, filtration and measurement in acetone medium and the determination range reported is 68–680 μg/ml. The color produced in the reaction with cerium(IV) sulphate [15] fades within 15 min. In addition, the proposed indirect method employs readily available and inexpensive chemicals unlike methods that utilize very expensive chemicals such as 3-methylbenzothiazole-2-one hydrazone hydrochloride [18,38]. The other advantages of this method over the previously described indirect spectrophotometric methods [21–23] are: (a) non-critical working conditions, the method involving Cr(VI)–metol [23] requires a careful control of pH and in the method using vanadium(V) [21] the reaction mixture is required to be heated in a boiling-water bath for 10 min before the absorbance of vanadium (IV) formed, is measured whereas the present method works well over a wide range of acid concentration and the reaction will be complete in cold condition; (b) wide range of linear response; (c) high sensitivity, ϵ value $\sim 1.2 \times 10^4$ l mol^{-1} cm^{-1} compared to $\sim 4 \times 10^3$ l mol^{-1} cm^{-1} in the previous method [23] and far less in the vanadium(V) method [21]; (d) low limit of detection with high accuracy and precision and (e) increased stability of the color system, 45–120 min as against only 15 min in the earlier method [21]. The two disadvantages of the present method compared to Cr(VI)–metol method [23] are: (a) more reaction time 15–30 min versus 5–15 min and (b) less stable colored

Table 2
Evaluation of accuracy and precision of the proposed method

Phenothiazine drug	Amount (μg)		Error (%)	RSD (%)	% Range of error	
	Taken	Found [a]			Confidence limits	
					$P = 0.05$	$P = 0.01$
CPH	120	118.6	−1.16	0.61	0.65	1.03
PH	100	98.83	−1.16	1.68	1.77	2.77
TPH	120	120.2	+0.16	0.73	0.77	1.20
TFPH	160	157.3	−1.66	0.91	0.96	1.50
FPH	160	161.0	+0.66	1.24	1.30	2.04
PCPMS	300	298.0	−0.66	1.04	1.09	1.71

[a] Average value of six determinations.

Table 3
Results of analysis of pharmaceutical preparations containing the studied phenothiazines

Drug and preparation [a]	Label claim, mg/tablet or mg/ml	Found [b]		Student's t-value [c]	F-value [d]
		Proposed method% recovery ± SD	BP method% recovery ± SD		
CPH					
CPH tablets (1)	25	99.7 ± 0.7	100.2 ± 0.6	1.22	1.36
Megatil tablets (2)	50	103.7 ± 0.7	102.8 ± 0.9	1.78	1.65
Emetil tablets[c]	100	100.3 ± 1.0	100.5 ± 1.3	0.28	1.69
Megatil injections (2)	25	100.7 ± 0.4	99.7 ± 0.6	3.16	2.25
PH					
Phenergan tablets (4)	25	100.5 ± 0.9	100.6 ± 1.1	0.16	1.49
Phena tablets (5)	10	101.9 ± 0.6	102.2 ± 0.8	0.68	1.78
Phenergan injections (4)	25	103.4 ± 0.4	103.0 ± 0.6	1.26	2.25
TPH					
Siquil tablets (6)	10	98.2 ± 0.5			
TFPH					
Trazine tablets (1)	10	98.7 ± 0.9	99.3 ± 0.6	1.26	2.25
Neocalm tablets (2)	10	99.0 ± 0.4	99.9 ± 0.6	2.85	2.25
FPH					
Prolinate injections (1)	25	100.9 ± 1.1	100.3 ± 0.8	1.00	1.89
Anatensol injections (6)	25	101.4 ± 0.8	101.0 ± 1.2	0.63	2.25
PCPMS					
Stemetil injections (4)	12.5	98.7 ± 0.9	99.3 ± 0.6	1.26	2.26

[a] Marketed by (1) Sun Pharma; (2) Intas; (3) LA Pharma; (4) Rhone-Poulenc; (5) Ind-Swift; (6) Sarabhai Chemicals.
[b] Average value of five determinations ± SD.
[c] Tabulated value at 95% confidence level is 2.78.
[d] Tabulated value at 95% confidence level is 6.39.

species, 45–120 min compared to > 24 h. However, these disadvantages do not mar the applicability of the method for routine analysis.

3. Experimental

3.1. Apparatus

Absorbance measurements were carried out using an Elico model SL171 digital spectrophotometer with glass cells of 10 mm path length.

3.2. Reagents and materials

Analytical-reagent grade chemicals and doubly distilled water were used throughout. A 1000 μg/ml potassium dichromate solution was prepared by dissolving 0.1 g of the reagent (S.d fine Chem. Ltd.) in distilled water and diluting to 100 ml in a calibrated flask. The solution was diluted further to get 50 μg/ml of potassium dichromate. Approximately 0.02 M ammonium ferrous sulphate solution was prepared by dissolving 7.8 g of the reagent (S.d Fine Chem. Ltd.) in distilled water in the presence of a few drops of dilute sulphuric acid. The solution was standardized [29] using potassium dichromate solution. Then, it was diluted to 1000 μg/ml. A 10 M hydrochloric acid was prepared by diluting 862 ml of concentrated acid (S.d. Fine Chem. Ltd.), Sp. Gr. 1.18 to one litre with distilled water. A 1.5 M ammonium thiocyanate solution was prepared by dissolving 11.5 g of the salt (Ranbaxy Lab Ltd.) in distilled water and diluting to 100 ml.

Pharmaceutical grade phenothiazines were gifted by several firms. Stock standard solutions containing 1000 μg/ml of each drug were prepared by dissolving weighed amount of chlorpromazine hydrochloride, CPH (British Pharm), promethazine hydrochloride, PH (Rhone-Poulenc), triflupromazine hydrochloride, TPH (Sarabhai Chemicals), trifluoperazine hydrochloride,

TFPH (SmithKline Beecham), fluphenazine hydrochloride, FPH (Sarabhai Chemicals) and prochlorperazine mesylate (methane sulphonate), PCPMS (Rhone-Poulenc) in distilled water. The solutions were kept in amber colored bottle and stored in a refrigerator. Working solutions of 200 μg/ml of PCPMS and 100 μg/ml in respect of others were prepared by appropriate dilution of the stock solution with distilled water.

3.3. General procedure

In each of a series of 10 ml calibrated flasks was placed 1 ml of 50 μg/ml potassium dichromate solution, followed by acidification by the addition of 1 ml of 10 M hydrochloric acid. After the addition of 0.25–1.75 ml of CPH or TPH, 0.25–1.50 ml of PH, 0.25–2.40 ml of TFPH, 0.25–2.50 ml of FPH (all 100 μg/ml) or 0.20–1.50 ml of PCPMS (200 μg/ml) solution, the overall volume was adjusted to 5 ml by the addition of requisite volume of distilled water. The flasks were let stand for 20–30 min depending on the individual phenothiazine drug (Table 1) with occasional shaking for the oxidation to complete as indicated by the complete disappearance of the purple or orange color of the radical cation. Subsequently, 1 ml of 400 μg/ml ammonium ferrous sulphate was added to each flask and mixed well. After one min, 1 ml of 1.5 M ammonium thiocyanate solution was added and the volume was made up to 10 ml and absorbance was recorded at 480 nm against distilled water blank. The concentration of each drug was found from a calibration graph constructed under the same conditions or the regression equation.

3.4. Procedure for preparations

3.4.1. Tablets

A known number of tablets were weighed and ground to a fine powder. A portion of the powder containing 100 mg of the active component was accurately weighed into a 100 ml calibrated flask, 60 ml of distilled water were added and shaken thoroughly for about 20 min to extract the drug. The contents were diluted to the mark, mixed well and filtered using quantitative filter paper to remove the insoluable residue. The filtrate was diluted to get 200 μg/ml of PCPMS and 100 μg/ml in respect of other drugs. A suitable aliquot of the diluted solution was analysed as described under general procedure.

3.4.2. Injections

The contents of known number of ampoules were mixed and an accurately measured volume equivalent to 100 mg of drugs was transferred into a 100 ml calibrated flask and diluted to the mark with distilled water. The solutions were diluted to get the working concentrations and analysed as described above.

Acknowledgements

The authors thank the Quality Control Managers of British Pharmaceuticals, SmithKline Beecham, Rhone-Poulenc and Sarabhai Chemicals, India, for their generous gift of pure samples of the drugs.

References

[1] J.E. Fairborther, Analysis of phenothiazine drugs, Pharm. J. 222 (1979) 271–275.
[2] H. Puzanowska-Tarasiewicz, J. Karpinska, Determination of phenothiazine drugs, Pharmazie 47 (1992) 887–892.
[3] British Pharmacopoeia, Her Majesty's Stationary Office, London, 1993.
[4] J.M. Garcia, A.I. Jimenez, F. Jimenez, J.J. Arias, Simultaneous determination of perphenazine and amitriptyline by derivative spectrophotometry, Anal. Lett. 25 (1992) 1511–1524.
[5] G. Wang, Ultra-violet spectrophotometric determination of flunarizine hydrochloride injection, Yaowu Fenxi Zazhi 11 (1991) 300–304.
[6] A. Chen, J. Han, HPLC determination of CPH injection, Quim. Anal. (Barcelona) 15 (1996) 326–333.
[7] M. Mathew, V. Dasgupta, C. Bethea, Quantitation of promethazine hydrochloride in pharmaceutical dosage forms using HPLC, Drug Dev. Ind. Pharm. 20 (1994) 1693–1698.
[8] O. Papp, I. Adma, I. Simonyi, Chromatographic purity tests of some phenothiazine derivatives, II. Gas chromatographic tests, Acta Pharm. Hung. 60 (1990) 204–211.
[9] F.A. Mohamed, Spectrofluorimetric determination of chlorpromazine hydrochloride and thioridazine hydrochloride, Anal. Lett. 28 (1995) 2491–2501.
[10] B. Dembinski, A. Szyldowska-Czerniak, M. Kurzawa, Determination of promazine hydrochloride in trace amounts by spectrofluorimetric method, Acta Pol. Pharm. 54 (1997) 415–419.
[11] S.A. Dermis, B. Uslu, Voltammetric determination of some phenothiazines using glassy carbon electrode, Port. Electrochim. Acta 15th March (1991) 5–15.
[12] Z.Q. Zhang, Z.G. Chen, H. Zhang, Adsorptive voltammetric determination of chlorpromazine in the presence of Triton-X-100, Microchem. J. 53 (1996) 282–289.
[13] H.D. Revanasiddappa, P.G. Ramappa, Spectrophotometric determination of some phenothiazine derivatives in pharmaceutical preparations, East. Pharm. 38 (1995) 127–129.
[14] M. Tarasiewicz, L. Kuzmicka, Determination of thioridazine by means of absorption spectrometry, Pharmazie 51 (1996) 189–190.
[15] T. Aman, A. Rashid, I. Khokhar, J. Iqbal, Spectrophotometric determination of chlorprormazine, Anal. Lett. 30 (1997) 109–119.
[16] K. Basavaiah, G. Krishnamurthy, Spectrophotometric assay of some antipsychotropic and anticholinergic phenothiazine drugs using ammonium molybdate, Anal. Lett. 31 (1998) 1037–1046.
[17] S.R. El-Shabouri, Diazocoupling determination of certain phenothiazine drugs with diazotized *p*-nitroaniline, Talanta 32 (1985) 999–1001.
[18] M.E. El-Kommos, K.M. Emara, Spectrophotometric determination of some phenothiazine drugs using 3-methyl benzothiazoline-2-one hydrazone, Analyst (London) 113 (1988) 1267–1271.
[19] N.A. Zakhari, M. Rizk, F. Ibrahim, M.I. Walash, Determination of phenothiazines by charge-transfer complex formation with chloranilic acid, Talanta 33 (1986) 111–114.
[20] K. Basavaiah, G. Krishnamurthy, Extractive spectrophotometric determination of some phenothiazine derivatives in pharmaceutical preparations, Talanta 46 (1998) 665–670.

[21] S. Singh, I.C. Shukla, S. Shukla, Photometric estimation of antiemetics with vanadium(V) reagent, Indian J. Pharm. Sci. 50 (1988) 278–279.
[22] K. Basavaiah, G. Krishnamurthy, J. Manjunatha Swamy, Indirect titrimetric and spectrophotometric methods for the determination of some phenothiazine psychotropics, Chem. Pharm. Bull. 47 (1999) 1351–1354.
[23] K. Basavaiah, J. Manjunatha Swamy, G. Krishnamurthy, Quantitation of pharmaceutically important phenothiazines by oxidimetry, Farmaco 55 (2000) 87–92.
[24] M.A. Raggi, V. Cavrini, A.M. Dipietra, Colorimetric determination of acetylcystein, penicillamine and mercaptopropionlyl glycine (tiopronin) in pharmaecutical dosage forms, J. Pharm. Sci. 71 (1982) 1384–1386.
[25] M.N. Reddy, D.G. Sankar, V.V. Sekhar, N. Ravindra, G.D. Rao, Spectrophotometric determination of some adrenergic agents using iron(III) and 1,10-phenanthroline, Indian Drugs 28 (1991) 331–333.
[26] L. Fu, Y. Ren, Determination of ascorbic acid in pharmaceutical products by flow injection spectrophotometry with iron(III)–1,10-phenanthroline, Fenxi Huaxue 20 (1992) 193–195.
[27] P.B. Issopoulos, P.T. Economou, Sensitive spectrophotometric determination of microamounts of penicillamine using an indirect redox technique, Anal. Chim. Acta 257 (1992) 203–207.
[28] F. Buhl, U. Hachula, Spectrophotometric determination of piramiden (aminopyrine) and novalgin (dipyrone) with iron(III)–1,10-phenanthroline system, Chem. Anal. (Warsaw) 29 (1984) 483–489.
[29] I.M. Kolthoff, R. Belcher, Volumetric Analysis, 1st edn., Interscience, New York, 1957, p. 177.
[30] E.B. Sandell, Colorimetric Determination of Traces of Metals, 3rd edn., Interscience, New York, 1959, pp. 524–536.
[31] Analytical Methods Committee, Recommendations for the definition, estimation and use of the detection limit, Analyst (London) 112 (1987) 199–204.
[32] F.D. Snell, C.T. Snell, C.A. Snell, Colorimetric Methods of Analysis, D. Van Nostrand Company, Inc. Princeton, New Jersey, Vol. IIA, 1959, p. 220.
[33] A.S. Issa, Y.A. Beltagy, M.S. Mohrous, Spectrophotometric determination of some phenothiazine derivatives and apipramol with chloramine-T, Talanta 25 (1978) 710–713.
[34] S.M. Hassan, F. Bela, F. Ibrahim, F.A. Aly, Colorimetric determination of some *N*-substituted phenothiazine derivatives using 2-iodobenzoate, Anal. Lett. 22 (1989) 1485–1498.
[35] A.F. Youssef, S.R. El-Shabouri, F.A. Mohamed, A.M.I. Rageh, Colorimetric determination of certain phenothiazine durgs by using morphine and iodine–potassium iodide reagents, J. Assoc. Off. Anal. Chem. 69 (1986) 513–518.
[36] C.S.P. Sastry, P.A.S.R. Tipirneni, M.V. Suryanarayana, Spectrophotometric determination of trimeprazine and methdilazine with sodium cobaltinitrite, East. Pharm. 32 (1989) 131–132.
[37] B. Dembinski, Colorimetric determination of promethazine, perazine, opipramol and noxiptyline by Rieinecke salt, Chem. Anal. (Warsaw) 32 (1987) 763–771.
[38] C.S.P. Sastry, P.A.S.R. Tipirneni, M.V. Suryanarayana, Spectrophotometric determination of some antiallargic agents with 3 methylbenzothiazoline-2-one hydrazone, J. Pharm. Biomed. Anal. 8 (1990) 287–292.