Indian Journal of Chemical Technology
Vol. 12, January 2005, pp. 25-29

Sensitive titrimetric and spectrophotometric assay methods for chlorpromazine with bromate-bromide mixture and two dyes

K Basavaiah*, P Nagegowda, H C Prameela & B C Somashekar

Department of Chemistry, University of Mysore, Manasagangotri, Mysore 570 006, India

Received 7 January 2004; revised received 4 October 2004; accepted 12 October 2004

Three new methods using titrimetry and spectrophotometry are described for the determination of chlorpromazine hydrochloride with bromate-bromide mixture as the oxidimetric-brominating agent and two dyes, methyl orange and indigo carmine. In titrimetry (method A), the drug is treated with a measured excess of bromate-bromide reagent in acid medium, and the residual bromine is determined iodometrically. The two spectrophotometric methods involve the addition of a measured excess of bromate-bromide mixture to drug solution in acidic conditions followed by estimation of the unreacted bromine by treating with a fixed amount of methyl orange (method B) or indigo carmine (method C) and measuring the absorbance at 520 nm (method B) or 610 nm (method C). Titrimetric procedure is applicable over 1-10 mg range and the reaction stoichiometry is found to be 1:1 (drug: bromate). In spectrophotometric methods, the systems obey Beer's law over 1.0-6.0 μg mL^{-1} and 2.5-15.0 μg mL^{-1}, for methods B and C, respectively. The molar absorptivity and Sandell sensitivity values and the limits of detection and quantification are reported for both spectrophotometric methods. The proposed methods were applied to the determination of chlorpromazine hydrochloride in tablets and injections with the assay results in the range of 98.63 to 101.88% of label claim. The reliability of the methods was assessed by parallel determination by the official method and by recovery studies.

Keywords: Chlorpromazine determination, titrimetry, spectrophotometry, bromate-bromide, dyes.

IPC Code: C07D 279/00; G01J 3/00; A61K

Chlorpromazine hydrochloride, CPH (Fig. 1) is a phenothiazine neuroleptic used for the control of psychoses including schizophrenia and mania, and severely disturbed or agitated behaviour. It is also used for the relief of nausea and vomiting, preoperative anxiety and intractable hiccups. The widespread use of this drug has necessitated the development of rapid, simple and precise methods for its quality control.

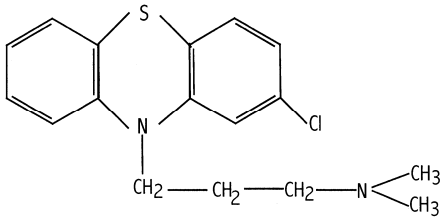

Fig. 1—Structure of chlopromazine

The procedures and techniques reported for phenothiazines including CPH have recently been reviewed[2]. Methods based on several techniques have been reported for the determination of CPH in the last one-decade. A few titrimetric procedures using dodecylpyridinium chloride[3], sodium hydroxide[4], tetrabutylammonium periodate[5], perchloric acid[6] and N-bromosuccinimide (NBS)[7] as titrants with spectrophotometric, pH-metric, potentiometric, oscillopolarographic and thermometric end point detection, respectively, have been reported for the assay in dosage forms. A variety of manual and automated visible spectrophotometric methods are based on either coloured complex formation or oxidation reaction yielding intensely coloured radical ion. CPH has been determined using bromocresol green[8], bromopyragallol red[9], chrome azurol S[10], eriochrome cyanine R[11], bromophenol blue[12], NBS-diphenylamine[13], cerium(IV)nitrate[14], N-bromophthalimide[15], sodium nitroprusside[16], dichromate[17], molybdate[18], chloramine-T[19] and hexacyanoferrate(III)[20] as reagents. Spectrofluorimetry[21] has also been used

*For correspondence (E-mail: basavaiahk@yahoo.co.in; Fax: 0091-821-2421263)

after oxidation by NBS in addition to room temperature phosphorimetry[22]. High performance liquid chromatography with UV-detection[23] and dual wavelength detection[24] has been proposed for tablets and injections. Other chromatographic techniques employed for the assay of CPH include liquid chromatography with UV-detection[25], thin layer chromatography (TLC) with densitometric detection[26] and high performance TLC with UV-detection[27]. Several papers describing UV-spectrophotometric[28] (stable regression), ion-selective electrode based potentiometric[29-31], voltammetric[32-34], polarographic[35], chemiluminescence spectroscopic[36] and electron spin resonance spectroscopic[37] methods for the determination of this neuroleptic drug have appeared in the last few years.

This work describes the use of bromate-bromide mixture and two dyes, methyl orange and indigo carmine for the titrimetric and spectrophotometric determination of CPH. Bromate-bromide mixture has been utilized extensively in the determination of a vast number of organic compounds, especially those of pharmaceutical interest[38-42]. Application of this reagent in this work, however, proved to be satisfactory since CPH can be determined on a micro scale with adequate accuracy and precision. Spectrophotometric methods, infact, are one of the most sensitive ever reported for CPH.

Experimental Procedure

Apparatus

A Systronics model 106 digital spectrophotometer with 1 cm quartz cells was used for absorbance measurements.

Reagents and solutions

All chemicals used were of analytical reagent grade and distilled water was used to prepare all solutions.

Bromate-bromide reagent

A 5 mM $KBrO_3$ –50 mM KBr mixture was prepared by dissolving accurately weighed 0.835 g of $KBrO_3$ (Sarabhai Chemicals, Baroda) and 5.95 g of KBr (Qualigens Fine Chem., India,) in water and diluting to 1 liter with water in a calibrated flask. This solution was used for titrimetric analysis and for spectrophotometric work, it was diluted appropriately to get 10 and 30 μg mL^{-1} $KBrO_3$, respectively, for methods B and C.

Methyl orange

A 500 μg mL^{-1} stock solution was prepared by dissolving 52.4 g of the dye (S. d. Fine Chem. India, dye content 85 %) in water and diluting to 100 mL in a calibrated flask, and filtered. The filtrate was diluted 10 fold with water to obtain 50 μg mL^{-1} methyl orange solution.

Indigo carmine

A 1000 μg mL^{-1} solution was prepared by dissolving 112 mg of the dye (S. d. Fine Chem, India, dye content 90%) in water and diluting to the mark in a 100 mL calibrated flask, and filtered. The filtrate was diluted 10 fold to get 100 μg mL^{-1} indigo carmine solution.

Sodium thiosulphate (0.03M)

Prepared by dissolving about 7.5 g of the chemical (S. d. Fine Chem, Mumbai) in 1 litre of water.

Potassium iodide (10%)

Prepared by dissolving 10 g of chemical (S. d. Fine Chem, Mumbai) in 100 mL water.

Starch indicator (1%)

About 1.0 g of soluble starch (S. d. Fine Chem, Mumbai) was dropped into 100 mL boiling water and cooled.

Hydrochloric acid (5 M)

Prepared by diluting 443 mL of concentrated acid (Qualigens fine Chem, Mumbai) Sp. gr. 1.18, to 1 litre with water.

Standard drug and sample solutions

A stock standard solution equivalent to 1 mg mL^{-1} CPH was prepared by dissolving requisite quantity of pure drug in water. Solutions of lower concentrations required for spectrophotometric work were prepared by appropriate dilution of stock solution. An amount of the finely ground tablet powder equivalent to 100 mg of CPH was accurately weighed into a 100 mL calibrated flask, 60 mL of water added and shaken for about 10-15 min. Then, diluted to the mark, mixed well and filtered. In the case of injections, an aliquot containing 100 mg of CPH was diluted to the mark in a 100 mL calibrated flask. The tablet extract and injection solution (1 mg mL^{-1}) were appropriately diluted for spectrophotometric assay.

Methods

Method A

A 10 mL aliquot of pure drug solution containing 1-10 mg of CPH was accurately transferred into an Erlenmeyer flask, and acidified by adding 5 mL of 5 M HCl. Ten mL of bromate-bromide mixture (5 mM w. r. t. $KBrO_3$) was pipetted into the flask and stoppered. The contents were mixed well and the flask was set aside for 5 min with occasional swirling. The stopper was then washed with 10 mL of water, and 5 mL of KI solution added. The liberated iodine was titrated with 0.03 M thiosulphate to a starch end point. A blank titration was performed under identical conditions, and from the amount of bromate reacted, the amount of CPH in the measured aliquot was calculated.

Method B

Aliquots of standard CPH solution (0.2-3.0 mL; 20 μg mL^{-1}) were delivered into a series of 10 mL calibrated flasks by means of a microburette followed by water to bring the total volume to 3 mL. The solution was acidified by adding 2 mL of 5 M HCl. To each flask was then added 1 mL of bromate-bromide reagent (10 μg mL^{-1} w. r. t. $KBrO_3$) and stoppered. After mixing the contents, the flasks were set aside for 15 min with occasional shaking. Finally, 1 mL of 50 μg mL^{-1} methyl orange solution was added to each flask, diluted to the mark with water, and absorbance measured at 520 nm against a reagent blank after 5 min.

Method C

Different aliquots, 0.5-3.0 mL of 50 μg mL^{-1} CPH solution were accurately measured into a series of 10 mL calibrated flasks followed by addition of water to bring the total volume to 3 mL. The solution was acidified by adding 2 mL of 5 M HCl to each flask. Then, 1.5 mL of bromate-bromide reagent (30 μg mL^{-1} w. r t. $KBrO_3$) was added, the flasks were stoppered and allowed to stand for 10 min with occasional shaking. Finally, 2 mL of 100 μg mL^{-1} indigo carmine solution was added to each flask, volume diluted to the mark with water, and absorbance measured at 610 nm against a reagent blank after 5 min.

For methods B and C, the calibration graph was prepared by plotting the absorbance against the drug concentration. The concentration of the unknown was read from calibration graph or calculated from the regression equation obtained from the Beer's law data.

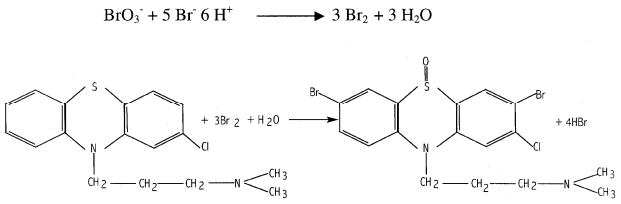

Fig. 2—Reaction scheme

Results and Discussion

An acidified mixture of bromate and bromide behaves as an equivalent solution of bromine and has been used extensively for the determination of inorganic and organic substances[43]. Preliminary experiments revealed that CPH is prone to both oxidation and bromination reaction by bromine generated *in situ* by the action of acid on bromate-bromide mixture.

Since the molar-ratio of the titrimetric reaction was found to be 1:1 (CPH: $KBrO_3$), it is probable that the drug undergoes both oxidation and bromination reactions as per the reaction scheme given in Fig. 2. The reaction was carried out in HCl medium, and the reaction stoichiometry was found to be unaffected when 2-9 mL of 5 M acid was used in a total volume of about 30 mL. Using 5 mM $KBrO_3$-50 mM KBr mixture, 1-10 mg of CPH can be conveniently determined.

In the proposed spectrophotometric methods, the ability of bromine to effect oxidation-bromination of CPH and irreversibly destroy methyl orange and indigo carmine to colourless products in acid medium has been exploited. Both methods are based on the oxidation-bromination of CPH by *in situ* generated bromine and subsequent determination of the latter by reacting with methyl orange or indigo carmine, and measuring the absorbance at 520 nm or 610 nm. In either method, the absorbance increased linearly with increasing concentration of CPH.

The Beer's law was obeyed in the concentration ranges given in Table 1. Correlation coefficients, intercepts and slopes for the calibration data are also compiled in Table 1. The graphs showed negligible intercept as described by the regression equation:

$$Y = a + b X$$

(where Y is the absorbance and X concentration in μg mL^{-1}) obtained by the method of least sequares. Other sensitivity parameters such as molar absorptivity, Sandell sensitivity and detection limit are also given

in Table 1 and indicate the high sensitivity of the methods.

Accuracy and precision

Within-day precision of the methods was determined by repeat analysis (n=7) of the standard solution containing the drug at three different levels. The RSD ranged from 0.28 to 1.34%. The day-to-day precision was established over a 5-day period on solutions prepared freshly each day. The low RSD values obtained (<2%) indicate the repeatability of the methods. Accuracy of the proposed methods was established by assaying solution of known amount/ concentration as done for determining the within-day precision. Relative error (%) values less than 1% indicate the high accuracy of the methods.

Table 1—Analytical parameters of spectrophotometric methods

Parameters	Method B	Method C
λmax (nm)	520	610
Beer's law limits (μg mL^{-1})	1.0-6.0	2.5 -15
Molar absorptivity (L moL^{-1}cm^{-1})	3.02×10^4	1.4×10^4
Sandell sensitivity (μg cm^{-2})	11.76	24.4
Limit of detection (μg mL^{-1})	0.14	0.24
Limit of quantification (μg mL^{-1})	0.45	0.79
Regression equation (Y*)		
Intercept, a	–0.003	–0.02
Slope, b	0.085	0.04
Correlation coefficient, r	0.9926	0.9896

*Y = a + bX, where Y is absorbance and X concentration in μg mL^{-1}

Application to formulations

The proposed methods were applied to the assay of CPH in four brands of tablets without any coated colour and two brands of injections. The results were in the range of 98.63 to 101.88% of label claim and were also checked by the official BP method[44]. There was close agreement between the results obtained by the proposed methods and the reference method as found from the Student's t-value and F-value. The results obtained by the proposed methods agreed well with the label claim in all instances. To further establish the validity of the methods, recovery tests via standard addition technique were performed on three samples. Pre-analysed formulations were spiked with pure CPH at three different levels and the total was found by the proposed methods. The experiment at each level was repeated three times. The percent recoveries of the pure drug added (Table 2) reveal that commonly added excipients such as lactose, talc, starch, alginate, stearate, gumacacia, calcium gluconate and calcium dihydrogen orthophosphate did not interfere in the assay methods.

Conclusions

The results obtained clearly demonstrate the suitability of using bromate-bromide mixture and two dyes for the micro determination of chloropromazine. The versatility and simplicity of the titrimetric technique employing bromate-bromide mixture is clear from a large number of pharmaceutical substances that were assayed. When the spectrophotometric methods are compared with other methods that measure the absorbance of either

Table 2—Results of recovery study using standard-addition method

Tablet brand name	Method A				Method B				Method C			
	Amount of drug in extract, mg	Amount of pure drug added, mg	Total found, mg	Recovery* of pure drug added, %	Amount of drug in extract, µg	Amount of pure drug added, µg	Total found, mg	Recovery of pure drug added, %	Amount of drug in extract, µg	Amount of pure drug added, µg	Total found, µg	Recovery* of pure drug added, %
Metagil	0.99	2.00	3.02	101.60	9.60	10.00	19.89	102.87	19.98	30.00	49.53	98.50
tablet	0.99	4.00	5.00	100.31	9.60	20.00	29.65	100.23	19.98	60.00	81.93	103.25
(50 mg)	0.99	6.00	6.95	99.33	9.60	30.00	39.18	98.61	19.98	90.00	107.85	97.63
Metagil	2.03	2.00	4.08	102.59	20.04	10.00	30.14	100.97	30.11	30.00	61.01	103.00
tablet	2.03	4.00	6.05	100.40	20.04	20.00	39.96	99.62	30.11	60.00	89.76	99.41
(100 mg)	2.03	6.00	7.88	97.53	20.04	30.00	49.72	98.94	30.11	90.00	119.62	99.46
Metagil	2.95	2.00	4.96	101.41	29.93	10.00	40.03	101.05	40.96	30.00	71.56	102.00
injection	2.95	4.00	6.95	100.10	29.93	20.00	49.99	100.33	40.96	60.00	99.85	98.15
(25mg/mL)	2.95	6.00	8.92	99.53	29.93	30.00	59.34	98.02	40.96	90.00	128.59	97.37

*Mean value of three determinations.

complex or radical cation, the proposed methods are superior interms of sensitivity, optimal conditions and stability of the colour measured. The procedures also show competitive accuracy and precision with other established techniques and allow the determination of the drug in pharmaceutical formulations. However, the methods are inferior to other techniques in selectivity.

Acknowledgement

The authors express their gratitude to the Quality Control Manager, British Pharmaceuticals Ltd., India, for providing pure sample of CPH as gift.

References

1 Martindale, *The Extra Pharmacopoeia,* 30th edn, edited by Reynolds J E F (The Pharmaceutical Press, London), 1993.
2 Puzanowska-Tarasiewicz H & Karpinska J, *Pharmazie,* 47 (1992) 887.
3 Borrego F, Sicilia D, Rubio S & Perez Bendito D, *Anal Chim Acta,* 362 (1998) 285.
4 Xu G, *Fenxi Shiyanshi,* 16 (1997) 17.
5 Douranghi Azar M H & Farhadi K, *Talanta,* 44 (1997) 1773.
6 Yao D, Lu Z & Gao H, *Yaowu Fenxi Zazhi,* 12 (1992) 48.
7 Abbasi U M, Siddiqui M & Bhangar M I, *J Chem Soc Pak,* 13 (1991) 242.
8 Basavaiah K & Krishnamuthy G, *Talanta,* 46 (1998) 665.
9 Starczewska B, *J Trace Microprobe Tech,* 16 (1998) 151.
10 Rychlovsky P, Nemcova I, Misorava H & Zanatova M, *Lab Rob Autorm,* 8 (1996) 213.
11 Starczewska B & Karpinska J, *Anal Lett,* 29 (1996) 2475.
12 El Kerdway M M, Moustafa M A, El Ashry S M & El Wazzi D R, *Anal Lett,* 26 (1997) 1669.
13 Mohammed A I M I, *Talanta,* 44 (1997) 1173.
14 Aman T, Rashid A, Khokar I & Iqbal J, *Anal Lett,* 30 (1997) 109.
15 El-Kerdawy M M, Hassan S M & El Ashry S M, *Mikrochim Act,* 108 (1992) 323.
16 Basavaiah K, Krishnamurthy G & Manjunatha Swamy J, *East Pharm,* 41 (1998) 107.
17 Basavaiah K, Manjunatha Swamy J, Charan V S, Chandrashekar U & Prameela H C, *East Pharm,* 44 (2001) 97.
18 Basavaiah K & Krishnamurthy G, *Anal Lett,* 31 (1998) 1037.
19 Basavaiah K, Manjunatha Swamy J & Krishnamurthy G, *Anal Lett,* 32 (1999) 2613.
20 Basavaiah K & Krishnamurthy G, *Anal Chim (Rome),* 89 (1999) 623.
21 Mohamed F A, *Anal Lett,* 28 (1995) 2491.
22 Kitude T, Kitamura K, Hayakawa J, Nakamoto E & Krishimoto N, *Anal Chem,* 67 (1995) 3806.
23 Kollmorgen D & Kraut B, *J Chromatogr Biomed Appl,* 707 (1998) 181.
24 Liang H, Miao H & Yu R, *Sepu,* 10 (1992) 100.
25 Mikami E, Yamada S, Noda N, Fujii Y, Kawamura N & Hayakawa J, *Iyakuhin Kenkyu,* 23 (1992) 185.
26 Li Z, Shi T & Wu J, *Yaowu Fenxi Zazhi,* 12 (1992) 47.
27 Corti P, Dreassi E, Politi N & Valoti M, *Pharm Acta Helv,* 66 (1991) 329.
28 Xu Y, *Fenxi Huaxue,* 20 (1992) 560.
29 Suzuki H, Nakagawa H, Mifune M & Saito Y, *Chem Pharm Bull,* 41 (1993) 1123.
30 Glukhova O I, Tkach V I & Tayganok L P, *Zh Anal Khim,* 49 (1994) 1025.
31 Kojlo A, *Anal Lett,* 30 (1997) 2353.
32 Zhang Z Q, Chen Z G, Yang Z G & Zhang H, *Microchem J,* 53 (1996) 282.
33 Moore J J, Nam G G, Pipes L C & Coury Jr. L A, *Anal Chem,* 66 (1994) 3158.
34 Lu Z G, Zhu J J, Li X, Yao D Q & Gao H, *Fenxi Huaxue,* 20 (1992) 1191.
35 Mynka A F, Yavorskaya L P & Sen'kiv N P, *Farm Zh (Kiev),* 3 (1992) 49.
36 Lopoz Paz J L & Townshend A, *Anal Commun,* 33 (1996) 31.
37 Minakata K, Suzuki O, Ishikawa Y, Seno H & Asano M, *Forensic Sci Int,* 50 (1991) 167.
38 Massashi Katumi A & Sayuri M, *Bunseki Kagaku,* 43 (1994) 505.
39 El Bardicy M G, El Saharty Y S & Tawakkol M S, *Talanta,* 40 (1993) 577.
40 Basavaiah K & Prameela H C, *Anal Bioanal Chem,* 376 (2003) 879.
41 Basavaiah K, Chandrashekar U, Prameela H C & Nage Gowda P, *Acta Ciencia Indica Chem,* 29 (2003) 25.
42 Basavaiah K & Prameela H C, *Science Asia,* 29 (2003) 147.
43 Kolthoff I M, Belcher R, Stenger V A & Matsuyama G, *Volumetric Analysis*, 1st edn, Vol. III (Interscience Publishers Inc., New York), 1957, 501.
44 *The British Pharmacopoeia,* Her Majesty's Stationery Office, London, 1998.