Rapid Method for Direct Determination of Some Phenothiazine Drugs Using Thermometric Titrimetry*

[1]U.M. ABBASI, [1]MUNAWWAR SIDDIQUI AND [2]M.I. BHANGAR
[1]*Institute of Chemistry, Univeristy of Sindh, Jamshoro,*
[2]*National Centre of Excellence in Analytical Chemistry,*
University of Sindh, Jamshoro, Pakistan

(Received 25th April, 1991, revised 6th September, 1991)

Summary: A simple, rapid and accurate milligram method for the determination of chloropromazine hydrochloride (stemetil), promethazine hydrcohloride (Phenergan), and triflupromazine hydrochloride (Stelazine) in the presence of excipients is described. The reaction is made selective to react with N-bromosuccinimide and the heat of reaction is used to determine the end point of the titration. The method has been applied to pure and pharmaceutical formulation. A comparison of the results obtained by using this method and the U.S.P. methods, shows no significant difference in the accuracy of the two techniques. The main advantages of the proposed method are less time taken, the potential for automation of the process and ability to carry out assay of single dosage form.

Introduction

Phenothiazine drugs are widely used as tranquilisers, antihistaminics, antiemetics and anticholinergic [1]. The methods described for the determination of phenothiazines are generally titrimetry [2], spectrophotometry [3,4], fluorimetry [5] amperometry [6], voltametry [7], polarography [8], gas liquid chromatography [9] and high performance liquid chromatography [10]. Most of these methods often necessitate the separation of the active ingredient prior to its determination and hence are time consuming. One of the main advantages of the thermometric method is the matrix effect that can be regarded as being relatively insignificant provided the reaction is chosen to be selective towards the active ingredient and that the matrix is thermally neutral [11]. In the present work, some phenothiazine drugs in pure form and in pharmaceutical preparations are determined thermometrically with well known brominating and oxidising agents, N-bromosuccinimide (NBS). Part of this work has also been reported earlier [12].

The thermometric analysis can be performed by measuring the heat liberated or absorbed during the chemical reaction. The energy change occuring in such reactions are stoichiometric, that is to say they are a measure of the analyte concentration. Practically it is unnecessary to measure the absolute heat of reaction, and in thermometric titration the cessation of heat liberation or absorption is taken as the indication of the equivalence point.

Results and Discussion

To examine the precision of the procedure, eleven analyses were performed, the method compares favourably in accuracy with standard U.S.P. methods. The average recoveries obtained by the proposed method ranged from 98% to 100% for the pure and dosage from drugs and standard deviations ranged from 1.0 to 0.4 which indicate high accuracy and precision of the method. The method is flexible with regards to the amount to be assayed and analytically acceptable results are obtained over the range, 5 to 25 mg of active ingredient. Twenty moles of NBS were consumed in phenergan, stelazine and largactil while twenty eight moles were consumed by Stemetil. Although its mechanism is not clear but the results are reproducible and quantitative, the reaction could be useful for quality control [19].

We consider that the potential scope of the thermometric method for routine assay makes it the superior method for the determination of drugs in commercial preparations such as tablets, syrups, drops and injections. The thermometric method is decidely easier and faster to use where each analysis takes hardly 3-5 minutes.

Experimental

Instrumentation

The instrument was devised as described previously [13]* with certain changes, that involved the

*Presented at Second National Chemistry Conference Karachi, 28-31 Dec. 1990.

Table 1: Assay of the pure test drug by thermometric titrimetry.

S. No.	Sample	Amount mg	Amount mg	Recovery %	Molar ratio	Standard deviation	Co-efficient of variation
1.	Stemetil (Prochlorpera dihydrogen meleate)	5.00	4.9	98.0			
		10.00	9.9	99.2			
		15.00	15.0	100.0	28	1.00	1.01
		20.00	19.9	99.5			
		25.00	24.8	99.2			
2.	Phenergan (Promethazine Hydrochloride)	5.00	5.0	100.0			
		10.00	9.9	99.2			
		15.0	14.9	99.3	20	0.42	0.42
		20.00	19.8	99.0			
		25.00	24.8	99.6			
3.	Largactil (Chloromazine Hydrochloride)	5.00	5.00	100.			
		10.00	9.9	99.0			
		15.00	14.9	99.6	20	0.56	0.56
		20.00	15.0	100.0			
4.	Stelazine	5.00	4.9	89.0			
		10.00	9.8	98.0			
		15.00	14.9	99.3	20	0.73	0.74

*Each reading is the average of 11 values quoted

Table 2: Comparison of results for amount of drug in dosage form by use of thermometric method and U.S.P. method of assay.*

S.	Sample	Range/ mg	Thermo metric recovery	Range/ mg	U.S.P. Method recovery %
1.	Stemetil injection	5-25	99.20	5-25	100.00
2.	Phenergan injection	5-25	99.40	100-	350 98.00
3.	Largactil injection	5-25	99.10	5-25	100.00
4.	Stelazine tablets	5-25	99.00	5-25	98.00

use of a d.c wheatstone bridge circuit with a thermistor (10 K ohm nominal resistance at 25°). The off-balance voltage of the bridge was monitered by feeding directly to a potentiometric recorder which had various ranges full scale deflection of 1-100 mv or by amplifying it using d.c operational amplifier of 10 times gain. For the accurate and precise delivery of the titrant and titrand a Mettler automatic titrator model DL 21 was connected with our instrument.

A known amount of sample was placed in the titration vessel and was stirred using a controlled constant speed mechanical stirrer, untill the thermal stability was achieved. The sample solution was titrated with standard NBS and the amount of the analyte determined from the enthalpogram.

Reagents

The reagents used were pure of analytical grade, purchased from Fluka (Switzerland). Other pharmaceutical preparations (Tablets and injections) such as largactil, stemetil, phenergan (May and Baker) and stelazine (SK&F), were obtained locally. The purity of Trifluoromazine (Sigma U.S.A.) was checked by taking melting point, mixed melting point, followed by ultra violet spectroscopy [14], thin layer chromatography and analysis by standard method [15].

N-Bromosuccinimide 0.02M

The titrant (0.356 g) was freshly prepared each time in 100 ml doubly distilled water and standardizing iodometrically [16].

Pure Sample Solution

Pure stemetil, largactil and phenergan were prepared by dissolving 100 mg in 100 ml of 0.15 M HCl solution while stelazine was prepared in 100 ml distilled water.

Tablets

Forty tablets, weighted and finely powdered. A known tablets (concentration range according to Table 2) was dissolved in required volume of 0.15M HCl or distilled water.

Ampoules Vials

Accurately measured valume of the preparation equivalent to the concentration range given in Table 2 was prepared in calibrated flask and proceeded as under pure sample.

Thermometric method of Assay

An aliquot of the solution containing 5-25 mg of drug (either pure or in dosage form) was placed in thermostated reaction vessel and titrant (NBS) was delivered at the nominal delivery rate of 2.7 ml. min^{-1}; the actual rate being determined gravimetrically. The equivalance point was obtained by extrapolation of the linear part of the graph before and after the curvature at the end point. The length of the trace corresponding to the volume of the titrant consumed was measured and the amount of sample solution was then calculated.

Official method of analysis

A known amount of either powdered tablets or accurately measured volume of solution taken from ampoules was dissolved in water and aliquots of the solution were assayed by the recommended U.S.P. method [17,18].

References

1. J.J. Lewis, An introduction to Pharmacology, 3rd Edition, pp. 251 Churchill Livingstone, Edinnburgh, 1965.
2. M.I. Walash, M. Rizk, A.M. Abu-Ouf and F. Belal, *Analyst*, **108**, 626 (1983).
3. A.G. Davidson, *J.Pharm.Pharmacol.*, **28**, 795 (1976).
4. M.E. El-Komos and K.M. Emara, *Analyst* 113, 1267 (1988).
5. T.J. Mellinger and C.E. Keeler, *Anal.Chem.*, **36**, 1840 (1964).
6. L. Wasilewska and E. Szyzszko, *Diss.Pharm.Pharmacol.*, **21**, 591 (1969).
7. G.J. Patriache, *Mikrochim.Acta.*, 950 (1970).
8. Z.F.W. Teare and S.I. Borst, *J.Pharm. Pharmacoe*, **21**, 277 (1969).
9. L. Laitem, I. Bello and P. Gaspar, *J. Chromatog.* 156, 327 (1978).
10. W.J. Allender and A.W. Archer, *J. Forensic Sci.*, **29**, 515 (1984).
11. L.S. Bark, S.M. Bark, Thermometric Titrimetry, Pergamon Press, Oxford, 1969.
12. U.M. Abbasi, F. Chand, M.I. Bhangar and S.A. Memon, *Talanta*, **33**, 173 (1986).
13. U.M. Abbasi and L.S. Bark, 4th International SAC Conference, 1977.
14. E.G.C Clark, Isolation and Identification of Drugs in Pharmaceutical, Body Fluids and Postmortem Materials, Pharmaceutical Press, London, 1974.
15. The {harmacopoeia of Japan, 9th Ed., Society of Japanese Pharmacopoeia, Yukuji Nippo Ltd., Tokyo, 1976.
16. M.Z. Barkat and M.F.A. El-Wahab, *Anal.Chem.*, **26**, 1973, (1954).
17. United States Pharmacopeia XII Revision, National Formulary XVI Edition United States Pharmacopeial Convention, Rockville, MD, 1985.
18. United States Pharmacopoeia XIX. Mack, Easton, PA, 1975.
19. V.N. Pathak, I.C. Shukla and S.R. Shukla, *Talanta*, **29**, 58 (1982).