

**ACID-BASE TITRIMETRIC ASSAY OF HYDROXYZINE
DIHYDROCHLORIDE IN PHARMACEUTICAL SAMPLES**

**NAGARAJU RAJENDRAPRASAD, KANAKAPURA BASAVAI AH* AND
KANAKAPURA BASAVAI AH VINAY**

Department of Studies in Chemistry, Manasagangothri, University of Mysore, Mysore-
570006, India

*Corresponding Author

Prof. K. Basavaiah, Department of Chemistry,
University of Mysore, Manasagangothri, Mysore-570 006, India.

E-mail: basavaiahk@yahoo.co.in, Phone: 9448939105.

ABSTRACT

Two simple titrimetric methods have been developed for the determination of hydroxyzine dihydrochloride (HDH) in pure form and in tablets. The principle of the methods are simple acid-base reactions in which the hydrochloride content of the drug was determined by titrating with an aqueous standardized NaOH solution either visually using phenolphthalein as indicator (method A) or potentiometrically (method B) using glass-calomel electrode system. The methods were applicable over the range of 2-20 mg HDH. The procedures were also applied for the determination of HDH in its dosage forms and the results were found in good agreement with those obtained by the reference method. The precision, expressed by intra-day and inter-day relative standard deviation values, was satisfactory ($RSD \leq 2.76\%$). The accuracy was satisfactory as well $RE \leq 2.67\%$. Excipients used as additives in pharmaceutical formulations did not interfere in the proposed procedures as shown by the recovery study *via* standard addition technique with recovery percentage in the range 97.48 – 106.3% with a standard deviation of 1.76 - 3.42 %.

Key words: Hydroxyzine dihydrochloride; determination; acid-base titrimetry; potentiometry; pharmaceuticals.

INTRODUCTION

Hydroxyzine dihydrochloride (HDH), chemically known as (*RS*)-2-{2-[4-(*p*-chlorophenylbenzyl)piperazin-1-yl]ethoxy}ethanol dihydrochloride, is a first-generation antihistamine of the piperazine class that is an H₁ receptor antagonist. It is widely used in the control of anxiety [1], treatment of branchial asthma and in some cases to relax patients before surgery [2-4].

Various available analytical methods in the literature reported for the determination of HDH in pharmaceuticals or biological fluids include high-performance liquid chromatography [5-9], gas chromatography [10], thin layer chromatography [11], micellar liquid chromatography [12], capillary zone electrophoresis [13, 14], voltammetry [15], LC-MS [16], potentiometry [17, 18], gravimetry [19] and visible spectrophotometry [20-24]. The official USP method is also available for the assay of the drug in tablets employs a chromatographic system equipped with a UV-detection, where HDH can be detected at 232 nm [25].

Although, chromatographic techniques have been suggested for the determination of HDH, it requires high skillful operator and the instrument is expensive and not available for most local manufacturers. The other procedures are time-consuming, involve multi steps, take long reaction time. In addition, most of the described procedures require expensive instrumental setup.

Some titrimetric procedures were also found in the literature for the assay of HDH. The method by Sanrick and Janik [26] involved the precipitation of the drug with sodium tetraphenylborate, filtration, dissolution of the precipitate in acetone and potentiometric titration with AgNO₃. The complexometric determination of HDH [27] also involved the precipitation of the drug with cadmium nitrate, filtration of the precipitate, and titration of the residual cadmium with EDTA. Basavaiah and Charan have reported two titrimetric procedures for the determination of HDH. One approach uses mercury(II) as titrant and diphenylcarbazone-bromothymol blue as indicator [21]. The other method [22] involved the precipitation of chloride with AgNO₃, filtration of the precipitate and titration of the excess AgNO₃ with thiocyanate using Fe(III) alum as indicator. The reported titrimetric procedures except the Hg(II) method, are indirect, involve multi steps, laborious and time-consuming. Even the direct titrimetric procedure

employing Hg(II) as titrant requires careful control of pH for the titration of chloride content of drug.

So, there is a need to develop simple, reliable, rapid and economical method for the determination of HDH in pharmaceuticals. The titrimetric procedure is very simple technique adoptable to determine the drug content in milligram level in the quality control laboratories across the developing countries where modern and expensive instruments are un available.

In this paper, two validated procedures are described for the determination of HDH without the need of all experimental operations as done in the reported methods [22, 26, 27]. The methods are based on the titration of the drug solution in neutral ethanol with aqueous NaOH to a phenolphthalein end point (method A) or potentiometric equivalence point (method B). The procedures offer several advantages, such as speed, simplicity, accuracy and precision, selectivity and cost-effectiveness, and consequently, it can be easily adapted by the quality control laboratories for routine analysis.

EXPERIMENTAL

Apparatus

A Elico 120 digital pH meter provided with a combined glass-SCE electrode system was used for potentiometric titration.

Reagents and Solutions

All chemicals used were of analytical reagent grade. Boiled-out and cooled distilled water was used through out the investigation.

Sodium hydroxide (~0.01 M): Accurately 0.2 g of the pure NaOH (Merck, India) was dissolved in bidistilled water. The solution was made up to 500 ml with bidistilled water and standardized [28].

Phenolphthalein indicator (0.5%): It prepared by dissolving 500 mg of the pure phenolphthalein powder (S.D's Lab Chem & Industries, Bombay) in 50 ml alcohol and diluted to 100 ml with bidistilled water.

Standard drug solution

Stock standard solution containing 2 mg ml⁻¹ drug was prepared by dissolving the required amount of HDH (UCB Pharma Ltd) in neutralized alcohol. Neutralized alcohol was prepared by adding dilute alcoholic KOH to ethanol with constant stirring to a phenolphthalein end point.

General Procedures

Visual Titration (Method A)

An aliquot of the drug solution containing 2.0-20.0 mg of HDH was measured accurately and transferred into a clean 100 ml titration flask and the total volume was brought to 10 ml with neutral alcohol. Then, 2 to 4 drops of 0.5 % phenolphthalein indicator were added and the solution was titrated with standard (0.01 M) sodium hydroxide solution to a pink colour end point.

A blank titration was performed and necessary volume corrections were made.

The amount of the drug in the measured aliquot was calculated from

$$\text{Amount (mg)} = VM_wR/n$$

where V = volume of NaOH required, ml; M_w = relative molecular mass of the drug; R = molarity of NaOH and n = number of moles of NaOH reacting with each mole of HDH.

Potentiometric Titration (Method B)

An aliquot of the standard drug solution equivalent to 2.0-20.0 mg of HDH was measured accurately and transferred into a clean 100 ml beaker and the solution was diluted to 25 ml by adding neutral alcohol. The contents were stirred magnetically and the titrant (0.01 M NaOH) was added from a microburette. Near the equivalence point, titrant was added in 0.05 ml increments. After each addition of titrant, the solution was stirred magnetically for 30 s and the steady potential was noted. The addition of titrant was continued until no significant change in potential on further addition of titrant. The equivalence point was determined by applying the graphical method. The amount of the drug in the measured aliquot was calculated as described under visual titration.

Procedure for Formulations

Atarax 25 and Atarax 10 (UCB Pharma Ltd) tablets, were used in the investigation.

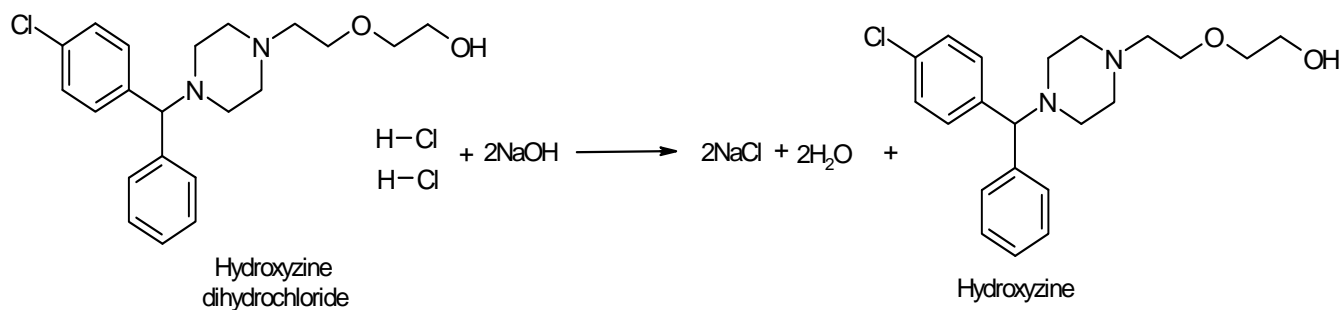
Twenty tablets were weighed and ground into a fine powder. An amount of powder equivalent to 200 mg of HDH was weighed accurately into 100 ml calibrated flask, 70 ml of neutral alcohol was added and shaken for about 20 min. Then the volume was made up to the mark with neutral alcohol, mixed well and filtered using Whatmann No 42 filter paper. The first 10 ml portion of the filtrate was discarded. A suitable aliquot was next subjected to analysis by titrimetry as described earlier.

RESULTS AND DISCUSSIONS

Mineral acid salts of weak nitrogen bases hydrolyze so extensively in aqueous or aqueous-alcoholic (water: alcohol) solution, that it is possible to titrate the liberated acid with a strong mineral base [29]. The Japanese Pharmacopoeia method [30] is an example for the titration of the hydrochloride salt of a water soluble base in aqueous medium with sodium hydroxide to the phenolphthalein end point. Titration of the hydrochloride salt of the drug in water against sodium hydroxide leads to the formation of water insoluble precipitate as the titration proceeds. To prevent precipitation, alcohol has been used in some procedures [31, 32]. Since alcohol is a base with respect to water as a solvent, dissolved bases react less strongly alkaline, their salts react more strongly acid, and the end points of the titrations are greatly sharpened. In our investigation, when aqueous solution of HDH was titrated with aqueous NaOH, white precipitate formed hampering the accurate location of the end point. However, no such problem was encountered when the drug solution in neutralized alcohol was titrated with aqueous NaOH. Alcoholic medium also enhanced the slope of inflection in the potentiometric titration curve besides improving the sharpness of phenolphthalein end point in visual titration.

Phenolphthalein gave satisfactory end point for the concentrations of analyte and titrant employed. The decrease in the values of potential was observed at the equivalence point with potentiometric end point detection (Fig. 1). With the two methods of equivalence point detection, a reaction stoichiometry of 1:2 (HDH : NaOH) was obtained which served as the basis for calculation. Using 0.01 M NaOH, 2.0-20.0 mg of HDH was conveniently determined. The relationship between the drug amount and the titration end point was examined. The linearity between the two parameters is apparent from the

correlation coefficients of 0.9985 and 0.9966 obtained by the method of least square for visual and potentiometric methods, respectively. From this, it is implied that the reaction between HDH and NaOH proceeds stoichiometrically in the ratio 1:2 in the range studied. The possible stoichiometric way of the neutralization between HDH and NaOH is depicted as follows:



Method Validation

Intra-day and inter-day accuracy and precision

The precision of the methods was evaluated in terms of intermediate precision (intra-day and inter-day). Three different amounts of HDH within the range of study in each method were analyzed in seven and five replicates in method A and method B, respectively, during the same day (intra-day precision) and five consecutive days (inter-day precision). For inter-day precision, each day analysis was performed in triplicate and pooled-standard deviation was calculated. The RSD values of intra-day and inter-day studies for HDH showed that the precision of the methods was good (Table 1). The accuracy of the methods was determined by the percent mean deviation from known concentration, and results are presented in Table 1.

Ruggedness of the methods

Method ruggedness was expressed as the RSD of the same procedure applied by four different analysts as well as using four different burettes. The inter-analysts RSD were within 2% whereas the inter-burettes RSD for the same HDH amounts was less than

about 2.2% suggesting that the developed methods were rugged. The results are presented in Table 2.

Application

The described titrimetric procedures were successfully applied for the determination of HDH in its pharmaceutical formulations (Atarax tablets of 10 and 25 mg HDH/tablet). The obtained results (Table 3) were statistically compared with those obtained by the official chromatographic method [25]. The reference method consists of chromatographic detection of HDH using UV-detector at 232 nm. The results obtained by the proposed methods agree well with those of reference method and with the label claim. The results were also compared statistically by a Student's t-test for accuracy and by a variance F-test for precision [33] with those of the reference method at 95 % confidence level as summarized in Table 3. The results showed that the calculated t-and F-values did not exceed the tabulated values inferring that proposed methods are as accurate and precise as the reference method.

Recovery Study

Accuracy and the reliability of the methods were further ascertained by performing recovery experiments. To a fixed amount of drug in formulation (pre-analysed): pure drug at three different levels was added, and the total was found by the proposed methods. Each test was repeated three times. The recoveries were in the range from 97.48 to 106.3% with the relative standard deviations of 1.76 to 3.42% indicating that commonly added excipients to tablets did not interfere in the determination. These results are compiled in Table 4.

CONCLUSIONS

Two simple, rapid, accurate and precise economical analytical methods were developed and validated. These two methods are more advantageous when compared to other published methods [5-16, 20-22]. The reported methods suffer from such drawbacks as high cost, multiple steps and also several clean-up steps (HPLC). They are time

consuming and often poorly reproducible, some requires organic toxic solvents. Any method chosen for routine analysis should be reasonably simple, used materials should readily available in the laboratory or readily obtainable, and require a minimum amount of equipment. These objectives have been fulfilled by the two titrimetric procedures developed. The accuracy, reproducibility, simplicity and cost-effectiveness of the methods suggest their application in the quality control laboratories where the modern and expensive instruments are not available.

ACKNOWLEDGEMENT

Authors thanks UCB Pharama Ltd, Mumbai, India, for gifting pure HDH. Two of the authors (NRP and KBV) thank the authorities of the University of Mysore, Mysore, for permission and facilities. NRP also thanks the University Grants Commission, New Delhi, India, for the award of a Meritorious Research Fellowship.

REFERENCES

- [1] M. Ferreri, E. G.Hantouche, *Acta Psychiatrica Scandinavica Supplementum*, **393** (1998) 102-108.
- [2] J. E. F. Reynolds, Martindale, *The Extra Pharmacopoeia*, 30th ed., The Pharmaceutical Press, London, 1993.
- [3] S. Khalid-Khan, M. Rynn, K. Rickels, *Generalised Anxiety Disorder*, Martin Dunitz, UK, 2002, p. 125.
- [4] S. V. Argyropoulos, J. J. Sandford, D. J. Nutt, *Pharmacol. Ther.* **88** (2000) 213-227.
- [5] S. E. Roberts, M. F. Delany, *J. Chromatogr.* **242** (1982) 364-368.
- [6] G. N. Menon, B. J. Norris, *J. Pharm. Sci.*, **70** (1981) 697-698.
- [7] A. N. Papas, S. M. Marchise, M. F. Delancy, *J. Liq. Chromatogr.* **2** (1984) 120-121.
- [8] B-B. Dragana, D. Rodulovic, D. Ivanovic, P. Ristic, *J. Pharm. Biomed. Anal.* **21** (1999) 15-22.
- [9] F. Pehoursq, *J. Pharm. Tox. Meth.* **50** (2004) 41-44.
- [10] P. Kintz, B. Godelar, P. Mangin, *Forensic Sci. Int.* **48** (1990) 139-143.
- [11] H. Ackermann, F. Kretzschmann, S. Kruger, B. Lexow, *Nahrung-Food* **21** (1977) 603-610.
- [12] C. Martinez-Algaba, J. M. Bermudez-Saldana, R. M. Villanueva-Camanas, S. Sagrado, M. J. Medina-Hernandez, *J. Pharm. Biomed. Anal.* **40** (2006) 312-321.
- [13] M. E. Capella-Peiro, A. Bossi, J. Esteve-Romero, *Anal. Biochem.* **352** (2006) 41-45.
- [14] K. Marzanna, D. Brunon, S-C. Aleksandra, *S. Pat, Acta. Pol. Pharma*, **56** (1999) 415-417.
- [15] A. M. Beltagi , O. M. Abdallah, M. M. Ghoneim, *Talanta* **74** (2008) 851–859.
- [16] Neng Zhou, Liang Yi-Zeng, Chen Ben-Mei , Ping Wang, Xian Chen, Liu Feng-Ping, *Chromatographia* **66** (2007) 481-486. ISSN 0009-5893.
- [17] A. Bouklouze, M. Elbouzekraoui, Y. Cherrah, M. Hassar, J. M. Kauffmann, *Electroanalysis* **14** (2002) 1369-1374.
- [18] L. L. Ciaccio, S. R. Missan, W. H. McMullen, and, T. C. Grenfeel, *Anal. Chem.* **29** (1957) 1670-1673.
- [19] J. Pasich, K. Stasiewska, *Acta. Pol. Pharm.* **19** (1962) 181-182.

- [20] R. T. Sane, U. M. Vaidya, V. G. Nayak, A. Y. Dhamankar, S. K. Joshi, V. J. Doshi, S. V. Sawant, V. B. Malkar, V. R. Pandit, A. Y. Sathe, S. Jukar, A. D. Nadakarni, *Indian drugs* **19** (1982) 398-403.
- [21] K. Basavaiah and V. S. Charan, *Acta Ciencia Indica* **27** (2001) 91-96.
- [22] K. Basavaiah, V. S. Charan, *Il Farmaco* **57** (2002) 9-17.
- [23] K. Basavaiah, V. S. Charan, *Ind. J. Pharm Sci.* **65** (2003) 660-662.
- [24] V. Nacea, L. Murgu, *Rev. Chem. (Bucharest)* **29** (1978) 577-579.
- [25] The US Pharmacopeia (USP 28), The National Formulary (NF 23), US Pharmacopeial Convention Inc., 2005, p. 982.
- [26] B. Sanrick, B. Janik, *Acta. Pol. Pharm.* **23** (1966) 573-575.
- [27] B. Dembinski, *Chem. Anal. (Warsaw)* **38** (1993) 183-187.
- [28] A Text-Book of "Quantitative Inorganic Analysis Including Elementary Instrumental Analysis", A.I. Vogel, London, 3 ed., The English Language Book Society and Longman, 1962, p.242.
- [29] A Text Book of Pharmaceutical Analysis, Edited by T. Higuchi, B-H. Einar, 1st Indian Edition, 1997, p. 387-388.
- [30] Pharmacopoeia of Japan, The, 6th ed, Ministry of Health and Welfare, Tokyo, 1951.
- [31] L. Saunders, R. S. Srivatsava, *J. Pharm. Pharmacol.* **3** (1951), 78-86.
- [32] British Pharmacopoeia Codex, 1954, Pharmaceutical Press, London, 1954.
- [33] J. Inczedy, T. Lengyel, A. M Ure. *IUPAC Compendium of Analytical Nomenclature : Definitive Rules*, Blackwell Science Inc, Boston 1998.

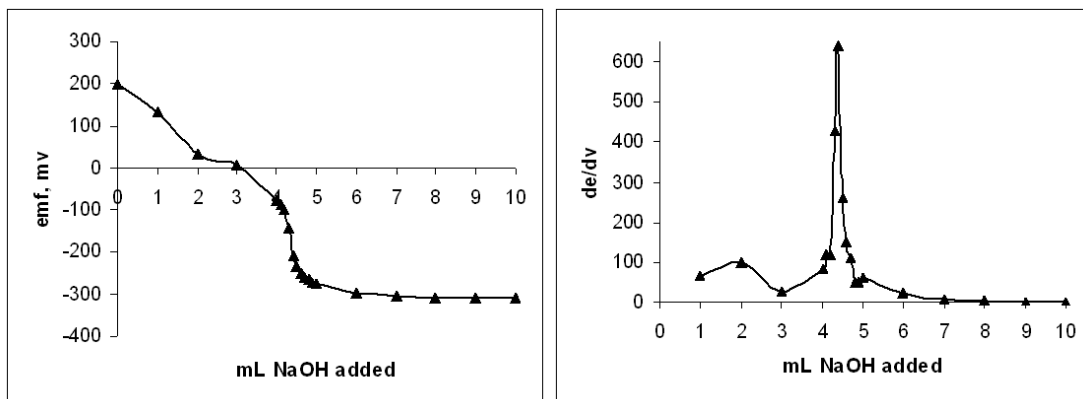


Fig.1. Potentiometric titration curves for 10 mg HDH Vs 0.01 M NaOH.

Table 1. *Intra-day and inter-day accuracy and precision data.*

Method	HDH taken, mg	Intra-day accuracy and precision			Inter-day accuracy and precision		
		HDH	RE,	RSD,	HDH	RE,	RSD,
		found, mg	%	%	found, mg	%	%
Visual titrimetry, (n=7)	4.0	3.95	1.25	1.96	4.06	1.52	2.56
	12.0	11.68	2.67	1.22	12.21	1.78	1.98
	20.0	19.66	1.70	0.86	20.43	2.14	1.15
Potentiometric titrimetry (n=5)	4.0	3.97	0.75	1.86	4.05	1.26	2.76
	12.0	11.86	1.17	1.35	12.17	1.38	0.99
	20.0	19.83	0.85	1.00	20.20	0.99	0.75

RE.relative error, RSD. relative standard deviation.

Table 2. Method ruggedness expressed as intermediate precision (% RSD)

Method	LMT taken, mg	Inter-analysts (%RSD), (n=4)	Inter-instruments (%RSD), (n=4)
Visual titrimetry	6.0	1.20	1.60
	12.0	1.56	2.20
	18.0	1.36	1.63
Potentiometric titrimetry	6.0	1.15	1.40
	12.0	1.05	1.10
	18.0	0.98	1.05

Table 3. Results of assay in tablets and comparison with official method.

Brand name	Label claim, mg/tablet	Found* (Percent of label claim \pm SD)		
		Official method	Proposed methods	
			Visual titrimetry	Potentiometric titrimetry
Atarax 25	25	99.12 \pm 1.06	98.64 \pm 1.46	100.1 \pm 1.12
			t =0.60	t =1.42
			F =1.89	F =1.12
Atarax 10	10	101.8 \pm 0.95	102.6 \pm 1.75	100.7 \pm 0.72
			t =0.94	t =2.08
			F =3.39	F =1.74

*Average of five determinations.

Tabulated t value at the 95% confidence level is 2.77.

Tabulated F value at the 95% confidence level is 6.39.

Table 4. Results of recovery study using standard addition method.

Tablet studied	Visual titrimetry				Potentiometric titrimetry			
	HDH in tablet extract, mg	Pure HDH added, mg	Total HDH found, mg	Pure HDH recovered (Percent \pm SD*)	HDH in tablet extract, mg	Pure HDH added, mg	Total HDH found, mg	Pure HDH recovered (Percent \pm SD*)
Atarax 25	7.89	4.0	11.79	97.48 \pm 1.76	8.01	4.0	12.15	103.6 \pm 2.46
	7.89	8.0	15.82	99.15 \pm 2.66	8.01	8.0	16.13	101.5 \pm 3.02
	7.89	12.0	20.10	101.7 \pm 2.54	8.01	12.0	20.05	100.3 \pm 1.98
Atarax 10	8.21	4.0	12.29	102.2 \pm 1.89	8.06	4.0	12.26	105.1 \pm 2.75
	8.21	8.0	16.55	104.3 \pm 2.68	8.06	8.0	16.56	106.3 \pm 3.42
	8.21	12.0	20.95	106.2 \pm 2.65	8.06	12.0	20.64	104.8 \pm 2.36

*Mean value of three determinations.