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Titrimetric Assay of Hydroxyzine Dihydrochloride in Pharmaceuticals and Formulations in Non-aqueous Medium

N. Rajendraprasad[1]*, K. Basavaiah[2]

[1]Department of Chemistry, J.S.S. College, Ooty Road, Mysore, Karnataka, India-570025
[2]Department of Chemistry, Manasagangothri, University of Mysore, India-570 006

Corres. author: prasadtnpur@yahoo.co.in; Phone: +91 9880547493

Abstract: Hydroxyzine, a piperazine H1-receptor antagonists effective in generalized anxiety disorder. Two simple, rapid, reliable, precise and accurate and cost-effective non-aqueous titrimetric procedures have been developed for the determination of hydroxyzine dihydrochloride (HDH) in bulk drug and its pharmaceutical formulations. The methods are based on the titration of the drug in glacial acetic acid in the presence of mercuric acetate with acetous perchloric acid to the visual end point using crystal violet as indicator and to the potentiometric end point. 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 to be in a good agreement with those obtained by the reference method. The precision results, expressed by intra-day and inter-day relative standard deviation values, were satisfactory (RSD ≤ 1.28 %). The accuracy was satisfactory as well (RE ≤ 1.33 %). 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 percentage recoveries in the range 97.75-101.5 % with a standard deviation of ≤ 1.52 %.
Keywords: Hydroxyzine dihydrochloride, Determination, Titrimetry and Pharmaceuticals.

INTRODUCTION

Hydroxyzine dihydrochloride (HDH), (*RS*)-2-{2-[4-(*p*-chloro-phenylbenzyl)piperazin-1-yl]ethoxy}ethanol dihydrochloride, (fig 1) is a piperazine antihistamine acting by diminishing the main action of histamine by competitive reversible blockade of histamine receptors sites H1 in the tissues. It is used in the treatment of branchial asthma, anxiety and in some cases to relax patients before surgery [1-3].

Various analytical methods have been reported for the analysis of HDH in pharmaceuticals and biological fluids. These include high-performance liquid chromatography [3-8], gas chromatography [9], thin layer chromatography [10], micellar liquid chromatography [11], capillary zone electrophoresis [12], voltammetry [13], LC-MS [14], potentiometry [15, 16], gravimetry [17] and visible spectrophotometry [18-25].

The titrimetric procedure is still in use for milligram determination of drug in formulations. Four titrimetric methods were found in the literature for the determination of HDH in pharmaceuticals. The method by Sanrick and Janik [26] involves the precipitation of the drug with sodium tetraphenyl borate, filtration, dissolution of the precipitate in acetone and potentiometric titration with $AgNO_3$. The complexometric determination of HDH [27] also involves the precipitation of the drug with cadmium nitrate, filtration of the precipitate, and titration of residual cadmium with EDTA. Basavaiah and Charan [19] proposed two titrimetric procedures for the determination of HDH in which one

approach uses mercury(II) as titrant and diphenylcarbazone-bromothymol blue as indicator and other involves [20] the precipitation of chloride with $AgNO_3$ and the residual $AgNO_3$ has been determined by back titrating with thiocyanate using Fe(III) as indicator. A two phase titrimetric assay [28] has also been reported for HDH by the present authors. Sodium lauryl sulphate was used as the titrant and dimethyl yellow as the indicator in the presence of chloroform and sulphuric acid. Since the method is ion pair extraction titration and do not produce more accurate results due to formation of emulsion and incomplete extraction of the product from one phase to another phase at and beyond the equivalence point. In another report of the present authors [29] the hydrochloride content of HDH has been titrated with alkali in hydro alcoholic medium. The assay has been carried out in neutral alcohol. The official USP method 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 [30].

The report of Ciaccio *et al* [16] involves the potentiometric determination of HDH in non-aqueous medium using 0.1 N $HClO_4$ as titrant in acetic acid. The method has been applied only for bulk sample and not for HDH in its formulations. Because HDH is dihydrochloride, the free base of HDH was obtained by washing a chloroformic solution of the drug with aqueous caustic, drying the free base over sodium sulphate, evaporation of chloroform and dissolving the residue in acetic acid before titration. Thus, the procedure involves multisteps and applicable only to macrosize samples.

Most of the reported methods require sample pre-treatment and extraction of the drug prior to the analysis, involve precipitation, filtration and titration of the unreacted precipitant and involve steps that are complex, tedious and time consuming. Further, many methods suffer from disadvantages such as inadequate accuracy and precision, critical working conditions and some requires sophisticated instruments or hazardous organic solvents.

In the present paper, two validated titrimetric procedures are described for the determination of HDH in pharmaceuticals and its formulations without any sample pretreatment or prior extraction. The methods are based on the basic property of the drug molecule in which the solution of drug and mercuric acetate in glacial acetic acid was titrated directly with acetous perchloric acid either visually to crystal-violet endpoint or potentiometrically using modified glass-saturated calomel electrode system. The methods, in addition to being rapid, sensitive, precise, gave satisfactory results when applied to formulations containing HDH. The results obtained in these methods were statistically compared, using analysis of variance. Additionally, the methods can be used in laboratories where modern and expensive instruments are not available.

MATERIALS AND METHODS

Apparatus

A Elico 120 digital pH meter provided with a combined glass-SCE electrode system was used for potentiometric titration. The KCl of the salt bridge was replaced with saturated solution of KCl in glacial acetic acid.

Reagents and Solutions

All chemicals used were of analytical reagent grade. All solutions are made in glacial acetic acid (S. D. Fine Chem, Mumbai, India) unless mentioned otherwise.

Perchloric Acid (0.01 M): The stock solution of (~0.1 M) perchloric acid (S. D. Fine Chem, Mumbai, India) was diluted appropriately with glacial acetic acid to get a working solution of 0.01 M perchloric acid and standardized with pure potassium hydrogen phthalate and crystal violet as indicator [31].

Crystal violet indicator (0.1 %):

Prepared by dissolving 50 mg of dye (S. D. Fine Chem, Mumbai, India) in 50 mL of glacial acetic acid.

Mercuric acetate solution (5 %):

Five gram of the pure $Hg(OAc)_2$ (Merck) was dissolved in 100 mL of glacial acetic acid, filtered and used.

Standard drug solution

Stock standard solution containing 1 mg mL^{-1} drug was prepared by dissolving the required amount of HDH (UCB Pharma Ltd) in glacial acetic acid.

General Procedures

Visual Titration (Method A)

An aliquot of the drug solution containing 2.0-20.0 mg of HDH was measured accurately and transfered into a clean and dry 100 mL titration flask and the total volume was brought to 10 mL with glacial acetic acid. Then, 2 mL of 5 % $Hg(OAc)_2$ was added, the content was mixed and after 2 min, two drops of crystal violet indicator were added and titrated with standard 0.01 M perchloric acid to a blue colour end point. The amount of the drug in the measured aliquot was calculated from

$Amount\ (mg) = VM_wR/n$

where V = volume of perchloric acid required, mL; M_w = relative molecular mass of the drug; and R = molarity of the perchloric acid and n = number of moles of perchloric acid 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 transfered into a clean and dry 100 mL beaker and the solution was diluted to 25 mL by adding glacial acetic acid followed by the addition of 2 mL of 5 % $Hg(OAc)_2$. The combined glass-SCE (modified) system was dipped in the solution. The contents were stirred magnetically and the titrant (0.01 M $HClO_4$) 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 there was 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 100 mg of HDH was weighed accurately into 100 mL calibrated flask, 70 mL of glacial acetic acid was added and shaken for about 20. Then the volume was made upto the mark with glacial acetic acid, 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 Discussion

The present methods are based on the neutralization reaction involving the basic property of HDH and employ two techniques.

Acetic acid displays acidic properties in dissociating to produce protons [32]:

$$CH_3COOH \longleftrightarrow CH_3COO^- + H^+$$

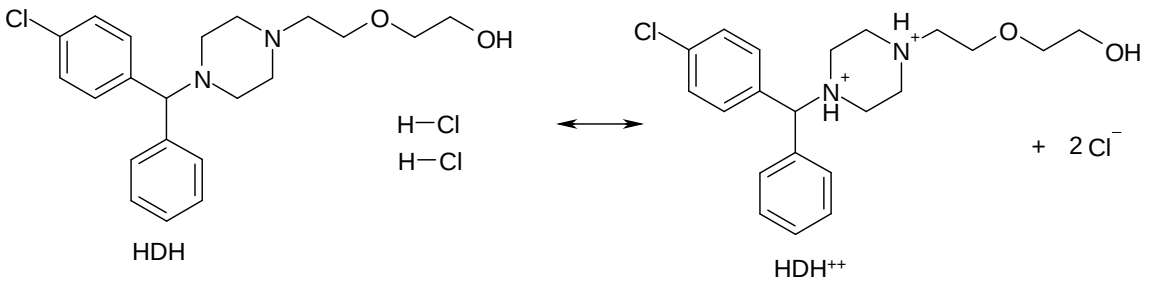
But in the presence of perchloric acid, a far stronger acid, it will accept a proton:

$$CH_3COOH + HClO_4 \longleftrightarrow CH_3COOH_2^+ + ClO_4^-$$

$$2CH_3COOH_2^+ + 2CH_3COO^- \longleftrightarrow 4CH_3COOH$$

The $CH_3COOH_2^+$ can very readily give up its proton to react with a base, so basic properties of a base is enhanced and hence, titration between weak base and perchloric acid can often be accurately carried out using acetic acid as solvent.

Since, the HDH is a dihydrochloride, which is very weakly basic, it cannot react quantitatively with acetous perchloric acid. In order to over come this problem, mercuric acetate was added (it remains undissociated in acetic acid solution) to HDH solution thereby causing the replacement of chloride ion by an equivalent amount of acetate ion, which serves as a strong base in acetic acid as shown in the scheme given below.



$$HDH^{++} + 2\,Cl^- + (CH_3COO)_2Hg + 2\,HClO_4 \longrightarrow HDH^{++}.2ClO_4^- + HgCl_2 + 2CH_3COOH$$

(undissociated) (undissociated)

:

Scheme. Possible reaction for the neutralization.

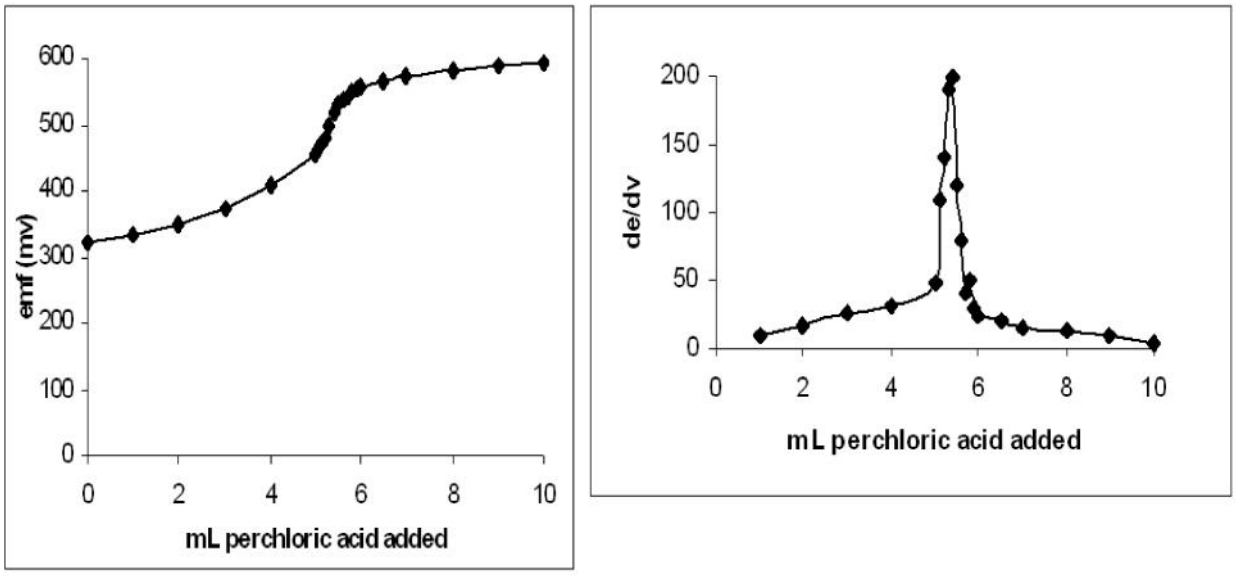


Figure 1: Potentiometric titration curves for 12 mg HDH *Vs* 0.01 M $HClO_4$.

The enhanced basicity of HDH in acetic acid medium is due to non-lavelling effect of acetic acid and the determination of HDH is very easier. The procedures involve the titration of HDH with perchloric acid with visual and potentiometric end point detection. Crystal violet gave satisfactory end point for the concentrations of analyte and titrant employed. A steep rise in the potential was observed at the equivalence point with potentiometric end point detection (Fig. 1). With both methods of equivalence point detection, a reaction stoichiometry of 1:2 (drug:titrant) was obtained which served as the basis for calculation. Using 0.01 M perchloric acid, 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 two parameters is apparent from the correlation coefficients of 0.9975 and 0.9976 obtained by the method of least squares for visual and potentiometric methods, respectively. From this it is implied that the reaction between HDH and perchloric acid proceeds stoichiometrically in the ratio 1:2 in the range studied.

Method optimisation

In both the methods, the optimum amount of mercuric acetate required was studied by varying its amount and fixing the drug amount constant followed by the measurement of the stoichometric amount of drug found in each case. It was found that, a 2 mL of 5 % $Hg(OAc)_2$ was sufficient for complete replacement of chloride in drug by acetate and the same amount was fixed through out the investigation.

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 analysed 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.**

Robustness and ruggedness of the methods

The robustness of the methods was evaluated by making small incremental changes in volume of $Hg(OAc)_2$ and the effect of the changes was studied by calculating the mg HDH found. The changes had negligible influence on the results as revealed by small intermediate precision values expressed as % RSD (< 0.95 %).

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 1.5 % whereas the inter-buretts RSD for the same HDH amounts was less than about 1 % suggesting that the developed method was rugged. The results are **shown in Table 2.**

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 found, mg	RE, %	RSD, %	HDH found, mg	RE, %	RSD, %
Visual titrimetry, (n=7)	6.0	6.03	0.5	1.28	6.08	1.33	1.20
	12.0	12.11	0.92	0.64	11.99	0.10	0.85
	18.0	18.13	0.72	0.42	17.98	0.11	0.56
Potentiometric titrimetry (n=5)	6.0	5.98	0.33	1.21	6.06	1.00	1.18
	12.0	12.06	0.5	0.72	12.03	0.25	0.82
	18.0	18.03	0.17	0.58	18.01	0.06	0.88

RE.relative error, RSD. relative standard deviation.

Table 2: Method robustness and ruggedness expressed as intermediate precision (% RSD)

Method	LMT taken, mg	Robustness	Ruggedness	
		Volume of $Hg(OAc)_2$*	Inter-analysts (%RSD), (n=4)	Inter-instruments (%RSD), (n=4)
Visual titrimetry	12	0.95	1.50	0.98
Potentiometric titrimetry	12	0.86	1.45	0.99

*The volume of Hg(OAc)2 varied were 1.5, 2.0 and 2.5 mL.

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

Brand name	Label claim, mg/tablet	Found* (Percent of label claim ± SD)		
		Official method	Proposed methods	
			Visual titrimetry	Potentiometric titrimetry
Atarax 25	25	99.1±1.39	101.52±2.78 **t**=1.83 **F**=4.0	100.56±1.56 **t**=1.56 **F**=1.26
Atarax 10	10	98.7±1.55	100.90±1.96 **t**=1.98 **F**=1.60	99.26±0.98 **t**=0.70 **F**=2.50

*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.

Visual titrimetry					Potentiometric titrimetry			
Tablet studied	HDH in tablet extract, mg	Pure HDH added, *mg*	Total HDH found, mg	Pure HDH recovered* %	HDH in tablet extract, mg	Pure HDH added, mg	Total HDH found, mg	Pure HDH recovered* %
Atarax 25	8.12	4.0	12.13	100.3±1.52	8.04	4.0	12.10	101.5±0.76
	8.12	8.0	16.01	98.63±0.85	8.04	8.0	16.06	100.3±0.92
	8.12	12.0	20.25	101.1±0.62	8.04	12.0	20.00	99.67±0.85
Atarax 10	8.07	4.0	12.00	98.25±1.46	7.94	4.0	11.85	97.75±0.62
	8.07	8.0	16.12	100.6±0.82	7.94	8.0	15.79	98.13±0.86
	8.07	12.0	20.04	99.75±1.04	7.94	12.0	19.87	99.42±1.12

*Mean value of three determination.

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 [30]. The reference method consisted that 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 results compiled in Table 4 show that recoveries were in the range from 98.72 to 101.52 % indicating that commonly added excipients to tablets did not interfere in the determination.

Conclusions

Several instrumental techniques [3-15] have been reported for the assay of hydroxyzine in pharmaceuticals and biological fluids. Some of the reported spectrophotometric and titrimetric methods [20-29] involve multisteps and the method [18] requires extraction and the reaction is pH dependant. The reported methods suffer from such draw backs 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 methods provide two simple procedures for the determination of HDH in pharmaceuticals and its dosage forms. 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.

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