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Acid-base titrimetric assay of pheniramine maleate in pharmaceuticals in hydro-alcoholic medium

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ABSTRACT

Two simple titrimetric methods are described for the determination of pheniramine maleate (PAM) in pure form and in its dosage forms. The principle involved in the methods are simple acid-base reaction in which the carboxylic acid group of the drug was determined by titrating with an aqueous NaOH solution either visually using phenolphthalein as indicator (method A) or pH-metrically (method B) using glass-calomel electrode system. The methods were applicable over the range of 2-20 mg of PAM. The procedures were applied to the determination of PAM in tablets, injections, 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 ≤ 2.58%). The accuracy was satisfactory as well (RE ≤ 2.14%). Excipients used as additives in pharmaceutical formulations did not interfere in the proposed procedures as shown by placebo blank and synthetic mixture analyses and also by the recovery study via standard addition technique with percentage recoveries in the range 97.48 – 106.3% with a standard deviation of 1.76 - 3.42%.

Keywords: Pheniramine maleate; assay; acid-base titrimetry; pH-metry; pharmaceuticals.

INTRODUCTION

Pheniramine maleate (PAM) ($C_{16}H_{20}N_2 \cdot C_4H_4O_4$), chemically known as N,N-Dimethyl-3-Phenyl-3-(2-pyridyl)propylamine hydrogen maleate (Fig 1) is an anti histamine H_1 receptor antagonist [1] used to treat allergic conditions such as hay fever. It has relatively strong sedative effects and may sometimes be used as an over- the counter sleeping pill in a similar manner to other sedating antihistamine.

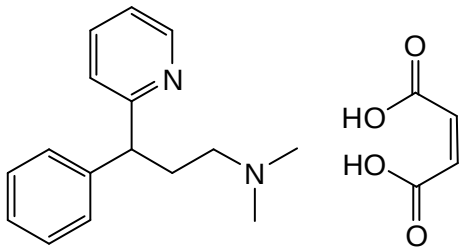


Figure 1. Chemical structure of PAM

Because of the wide use of PAM several techniques have been reported for its assay in pharmaceuticals as well as in biological fluids. PAM is officially listed in British Pharmacopoeia [2] and United States Pharmacopeia [3] which

recommend non-aqueous titration with perchloric acid as titrant where the end point was located either visually using crystal violet [2] as indicator or potentiometrically [3].

The methods for the assay of PAM in biological materials include high-performance liquid chromatography (HPLC) [4] and gas chromatography-mass spectrometry [5], where as methods like HPLC [6-13], thin layer chromatography [14], polarography [15] and capillary electrophoresis [16, 17] have been used for the assay of PAM in pharmaceuticals.

In spectroscopic quantification, UV [18] and visible spectrophotometric methods have been reported in the literature. In UV method the iron (III) complex of drug was measured at 273 nm in water whereas, the visible method [19] involved peroxidation of quercetin, a flavonol, with N-bromosuccinimide (NBS) followed by the formation of ion-pair complex with PAM and measurement of absorbance was measured at 528 nm. Though both the reported spectrophotometric methods sound sensitive they suffer from one or the other hurdle like pH control or liquid-liquid extraction step with organic solvents.

Titrimetry is still widely used in analytical chemistry for its superior speed and simplicity with a little compromise in accuracy and precision. Moreover, the instrumental methods are generally not as accurate and precise as the titrimetry in microanalysis. To the best of our knowledge, no titrimetric method is available for the quantification of PAM in pharmaceuticals, except the official methods which require vigorously anhydrous medium for accurate results.

In this paper, two titrimetric methods are presented for the assay of PAM in pure drug and in dosage forms. The methods involve the titration of the drug solution in neutral ethanol with aqueous NaOH to a phenolphthalein end point (method A) or pH-metric equivalence point (method B) using the glass modified saturated calomel electrode (SCE)system. The procedures offer several advantages, such as speed, simplicity, accuracy and precision, selectivity and cost-effectiveness, and consequently, they can be easily adapted by the quality control laboratories for routine analysis.

MATERIALS AND METHODS

2.1 Apparatus

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

2.2 Reagents and Solutions

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

2.2.1 Sodium hydroxide (~0.1 M)

Accurately weighed 2g of the pure NaOH (Merck, India) was dissolved in water, the solution was made upto 500 mL with water and was standardized [20] and diluted to working concentration of 0.012 M NaOH

2.2.2 Phenolphthalein indicator (0.5%)

Prepared by dissolving 500 mg of the pure phenolhthalein powder (S.D's Lab Chem & Industries, Bombay) in 50 mL alcohol and diluted to 100 mL with water.

2.2.3 Standard drug solution

Stock standard solution containing 2 mg mL^{-1} drug was prepared by dissolving the required amount of PAM (Sanofi Aventis Pharma., Mumbai, India,) in neutralized alcohol. Neutralised alcohol was prepared by adding dilute alcoholic KOH to ethanol with constant stirring to a phenolphthalein end point.

2.3 General Procedures

2.3.1 Visual Titration (Method A)

An aliquot of the drug solution containing 2.0-20.0 mg of PAM 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 drops of 0.5%

phenolphthalein indicator was added and the solution was titrated with standard (0.012 M) sodium hydroxide solution to a pink color end point.

An indicator blank titration was performed and necessary volume corrections were made.
The amount of the drug in the measured aliquot was calculated from

Amount (mg) = VM_wR/n

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

2.3.2 pH- metric Titration (Method B)
An aliquot of the standard drug solution equivalent to 2.0-20.0 mg of PAM was measured accurately and transferred into a clean 100 mL beaker and the solution was diluted to 25 mL by adding neutral alcohol. The content was stirred magnetically and the titrant (0.012 M NaOH) was added from a microburette. Near the equivalence point, titrant was added in 0.1 mL increments. After each addition of titrant, the solution was stirred magnetically for 30 s and the steady pH was noted. The addition of titrant was continued until there was no significant change in pH 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.

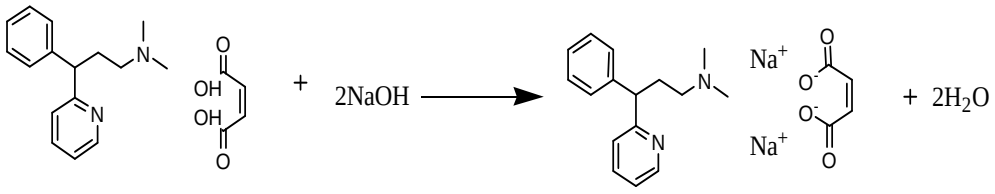
2.4 Assay procedure for Formulations
2.4.1 Tablets
Avil 25 and Avil 50 (Aventis Pharma Limited) tablets were used in the investigation. Twenty tablets were weighed and ground into a fine powder. An amount of powder equivalent to 200 mg of PAM was weighed accurately into 100 mL calibrated flask; 70 mL 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.

2.4.2 Injections
Five injection ampoules were withdrawn and mixed together. 10.0 mL of Avil injection (1 mL injection equivalent to 22.75 mg of PAM) was accurately measured and taken in to 100 mL volumetric flask, 70 mL of neutral alcohol was added and shaken well. Then the volume was made up to the mark with neutral alcohol (2.28 mg mL^{-1}PAM). A suitable aliquot was next subjected to analysis by titrimetry as described earlier.

RESULTS AND DISCUSSION

Mineral acid salts of weak nitrogen bases hydrolyze so extensively in aqueous or hydro-alcoholic solution, that it is possible to titrate the liberated acid with a strong mineral base [21]. Titration of the maleate salt of the drug in water against the sodium hydroxide leads to the formation of water turbidity as the titration proceeds. To prevent this precipitation, alcohol has been used in some procedures [22 -24]. Since alcohol is basic 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 PAM was titrated with aqueous NaOH, the turbidity was 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 pH-metric 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 pH was observed at the equivalence point with pH-metric 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 0.012 M NaOH, 2.0-20.0 mg of PAM 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 0.9999 for both methods. From this it is implied that the reaction between PAM and NaOH proceeds stoichiometrically in the ratio 1:2 in the range studied. The possible stoichiometric way of the neutralization between PAM and NaOH is depicted as follows:



Pheniramine maleate

Pheniramine di-sodium maleate

Method Validation

4.1 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 PAM within the range of study in each method were analyzed in five replicates in method A and method B, 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 PAM 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.

4.2 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 1.28%.whereas the inter-burettes RSD for the same PAM amounts was less than about 1.42% suggesting that the developed methods were rugged. The results are presented in Table 2.

4.3 Application

The described titrimetric procedures were successfully applied to the determination of PAM in its pharmaceutical formulations (Avil tablets of 25 and 50 mg PAM/tablet and Avil injection). The results obtained (Table 3) were statistically compared with those of an official method [2] which consisted of titration of acetous solution of tablets with acetous perchloric acid as titrant and the end point being located visually using crystal violet indicator. The results obtained by the proposed methods agreed 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 [25] 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.

4.4 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.

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

Method	PAM taken, mg	Intra-day accuracy and precision			Inter-day accuracy and precision		
		PAM found, mg	RE, %	RSD,%	PAM found, mg	RE,%	RSD, %
Visual titrimetry, (n=7)	4.0	3.95	1.25	1.96	4.05	1.46	2.36
	12.0	11.68	2.67	1.22	12.22	1.85	2.58
	20.0	19.66	1.70	0.86	20.42	2.14	2.26
pH-metric titrimetry (n=5)	4.0	3.97	0.75	1.86	4.06	1.68	2.36
	12.0	11.86	1.17	1.35	12.22	1.88	1.98
	20.0	19.83	0.85	1.00	20.33	1.67	1.87

RE-relative error, RSD- relative standard deviation.

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

Method	PAM taken, mg	Inter-analysts (%RSD), (n=4)	Inter-instruments (%RSD), (n=4)
Visual titrimetry	6.0	1.28	0.76
	12.0	0.84	1.08
	18.0	1.18	1.36
pH-metric titrimetry	6.0	1.08	1.42
	12.0	0.76	0.92
	18.0	1.32	1.36

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

Brand name	Label claim[a],	Found* (Percent of label claim ± SD)		
		Official method	Proposed methods	
			Visual titrimetry	pH-metric titrimetry
Avil 25	25	99.67±0.84	98.24±1.46 **t**=1.07 **F**=3.02	100.1±1.12 **t**=0.45 **F**=1.77
Avil 50	50	100.6±0.72	98.84±1.66 t=1.13 F=5.31	99.88±1.06 t=1.01 F=2.16
Avil injection	22.75	101.2±1.03	102.6±1.75 **t**=1.11 **F**=2.88	100.7±0.72 **t**=0.72 **F**=2.04

**Average of five determinations.*
[a] mg/tablet in tablets and mg/ml in injection.
Tabulated t value at the 95% confidence level is 2.77.
Tabulated F value at the 95% confidence level is 6.39.

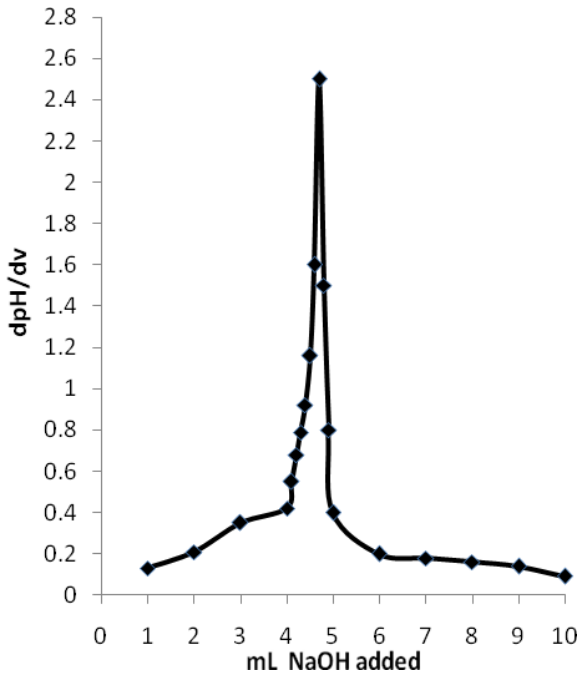


Figure2; pH- metric titration curve for 10 mg PAM Vs 0.012 M NaOH

Table 4. Results of recovery study using standard addition method

	Visual titrimetry				pH-metric titrimetry			
Tablet studied	PAM in tablet extract, mg	Pure PAM added, mg	Total PAM found, mg	Pure PAM recovered (Percent±SD*)	PAM in tablet extract, mg	Pure PAM added, mg	Total PAM found, mg	Pure PAM recovered (Percent±SD*)
Avil 25	7.86	4.0	11.79	97.48±1.76	8.01	4.0	12.15	103.6±2.46
	7.86	8.0	15.82	99.15±2.66	8.01	8.0	16.13	101.5±3.02
	7.86	12.0	20.10	101.7±2.54	8.01	12.0	20.05	100.3±1.98
Avil injection	8.21	4.0	12.29	102.2±1.89	8.06	4.0	12.26	105.1±2.75
	8.21	8.0	16.55	104.3±2.68	8.06	8.0	16.56	106.3±3.42
	8.21	12.0	20.95	106.2±2.65	8.06	12.0	20.64	104.8±2.36

**Mean value of three determinations.*

CONCLUSION

Two simple, rapid, accurate and precise and most economical analytical methods were developed and validated. These two methods are more advantageous when compared to other published methods. 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 require toxic organic solvents. Any method chosen for routine analysis should be reasonably simple, used materials should be 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.

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