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Research Article

A VALIDATED TITRIMETRIC METHOD FOR THE DETERMINATION OF PHENIRAMINE MALEATE IN PURE FORM AND IN THEIR PHARMACEUTICAL FORMULATION

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ABSTRACT

A simple, convenient and accurate visual titrimetric method for the determination of Pheniramine maleate (PM) in pure form and in their pharmaceutical formulations Avil (tablet and injection) using Pyridinium fluoro chromate (PFC) as an oxidant is described. The titrimetric method is based on the oxidation of the drugs in sulphuric acid medium by known excess of Pyridinium fluoro chromate and iodometric determination of the unreacted Pyridinium fluoro chromate(PFC). To examine the accuracy and precision of results percentage error, standard deviation(SD) and coefficient of variation (CV) were also calculated for each sample. Proposed method was validated by recovery analysis by drug addition method of drug.

Keywords: Pheniramine maleate(PM), Pyridinium fluoro chromate(PFC), iodometric titration, validation.

INTRODUCTION

Pheniramine maleate (PM) is an antihistamine drug of first generation having molecular formula $C_{16}H_{20}N_2.C_4H_4O_4$ and is chemically known as N,N-dimethyl-3-phenyl-3-(2-pyridyl) propylamine hydrogen maleate(Figure 1). First synthesis of this Pheniramine was done by Sperber et al[1] in year 1951.It is an alkylamine derivative and acts as histamine H1 antagonists by inhibiting the effect of histamine on capillary permeability, gastric secretion, contraction of bronchiolar and gastrointestinal smooth muscle[2-3]. This drug Pheniramine maleate is used to treat allergic conditions, sneezing, eye irritation, itching mainly to cure motion sickness, nausea, vomiting, hay fever or urticaria, rhinitis, pruritus and vertigo[4]. It is an important component of eye drops used for the treatment of allergic conjunctivitis. Various methods are available for the determiantion of Phenirmine maleate. The official method for the determination of Pheniramine maleate (PM), by using reagent perchloric acid through non aqueous titration has been described by British Pharmacopoeia[5] and United State Pharmacopeia[6]. The researcher's Clair et al[7] have determined Pheniramine maleate (PM) by employing oxidant perchloric acid thorough visual titration method. By using visual and potentiometric titration technique researcher's K. Basavaiah et al[8] have reported two methods for the determination of Pheniramine maleate (PM) in pure form and in its pharmaceutical preparations. K.Basavaiah et al[9] have reported two spectrophotometric techniques for the determination of pheniramine maleate (PM) in pure and in dosage form with sodium hypochlorite as an oxidant. Assay determination of pheniramine maleate (PM) by using UV-spectrophotometer was reported by Abdel Farrah et al[10] Visible spectrophotometric method have been employed by Mohammed et al[11] for the determination of pheniramine maleate (PM). High phase liquid chromatographic (HPLC) have been introduced by Taomin Huang et al[12] for the determination of Pheniarmine maleate in bulk and in its pharmaceutical formulations. Researcher S.P. Subramaniyan and S.K. Das[13] estimated quantification of pheniramine maleate by using thin layer chromatography (TLC).

Although at today, there are number of instrumental methods available for the determination of drugs but these methods are not as accurate and precise as the titrimetry in microanalysis. Beside this, these sophisticated instruments require proper calibration and handling due to their sensitiveness which is not easily possible at all laboratories of country like India and other developing countries due to high expenses. The main aim of this research paper is to develop a simple, rapid, cost effectiveness, non sophisticated, accurate and precise technique i.e. visual titration (Volumetric titration) by using mild and versatile oxidant like Pyridinium fluoro chromate (PFC) for the determination of pheniramine maleate drug in pure form and in their pharmaceutical preparations for the routine quality analysis of pharma industries.

MATERIAL AND METHOD

Reagents and solutions

Pyridinium Fluorochromate (0.03 N) solution was prepared by dissolving 0.497 gm of PFC in 150 ml glacial acetic acid (Merck) and made up the volume with distilled water in 250 ml volumetric flask. The prepared solution was standardised iodometrically with standard Sodium thio sulphate solution using starch as an indicator. Similarly (0.01N) stock solution of Sodium thio sulphate was prepared by dissolving 3.16 gm of sodium thio sulphate (Unhydrous) AR grade of Hi Media in distilled water of 1000 ml volumetric flask and made up to the mark with distilled water. This stock solution was standardised by using 0.01 N potassium dichromate (Moly Chem) solution iodometrically by using starch as an indicator. Stock solution of (0.01 N) Potassium Dichromate was prepared by dissolving 0.245 gm of $K_2Cr_2O_7$ (A.R Grade of Moly Chem) in distilled

water of 500 ml volumetric flask. Similarly solution of Potassium Iodide (10%) and starch solution (1%) W/V were also prepared in double distilled water.

Preparation of drug solution
Pure solution of Pheniramine maleate (PM)

Pure Solution of Pheniramine maleate (PM) was prepared by taking 100 mg pure compound of Pheniramine maleate (PM) supplied on request, as gift sample by Sanofi India Ltd, Ankleshwar, Distt-Bharuch, Gujarat, India in 100 ml volumetric flask and first dissolved it in minimum quantality of distilled water. The solution of volumetric flask has been shaken thoroughly for few minutes so that compound may dissolve properly. After getting a homogenous solution the flask was made up to the mark with distilled water.

Solution of pharmaceutical preparation
For tablet Avil- 25 mg

The 20 tablets of Avil- 25 mg manufactured by Sanofi India Ltd, Ankleshwar, Distt-Bharuch, Gujarat, India has been obtained from local commercial source and these tablets were ground into a fine power. The powder equivalent to 100 mg of sample, was taken in 100 ml calibrated flask and dissolved in the same process as described above for the pure solution of PM.

For an injection Avil-10 ml

The contents of 20 ampoules Avil-10 ml injection manufactured by Sanofi India Ltd, Ankleshwar, Distt-Bharuch, Gujarat, India were mixed properly and volume of injection equivalent to 100 mg of the pure sample were taken and diluted up to the mark with distilled water in 100 ml calibrated flask, so that concentration of flask become 1mg/ml.

General procedure: Aliquots of drug samples containing 1 to 5 mg were taken in 100 ml stoppered conical flask (Iodine flask) and to this 5 ml of 0.03 N PFC reagent (Prepared in 60% acetic acid) was added to it. Afterward 10 ml of 5N sulphuric acid was added to same reaction mixture of said flask. There after reaction mixture was shaken thoroughly, in order to mix the contents of flask properly and kept to stand the whole solution of flask for required reaction time at room temperature (25-30^{o}C) so that reaction between the contents of flask may be completed. After the completion of reaction 5 ml of 10% KI was added to same reaction mixture and whole reaction mixture was shaken properly and again allowed to stand for one minute. The unconsumed PFC was determined by iodometric titration by using starch as an indicator. Similarly blank experiment was also performed using all the regents under identical condition except the drug sample. The amount of PFC consumed for the given drug sample was calculated by the difference in the titre values of sodium thio sulphate solution for blank and actual experiment. The recovery of the drug sample was calculated with the amount of PFC consumed for the sample. Later on for accuracy and precision percentage error, coefficient of variation and standard deviation of each drug sample were calculated. Finally Standard Drug addition method was also performed to validate the authenticity of the method.

Expressions used in calculation: The expression used to determine the amount of drug present in the measured aliquot for each experiment is as follows:

$$\text{Weight (mg) of sample} = M_W \times N(V_B - V_S) / n$$

here,
M_W = Molecular weight of the sample, N = Normality of sodium thiosulphate solution, V_B = Volume of sodium thiosulphate solution for blank, V_S = Volume of sodium thiosulphate solution for sample, n = Stoichiometry of the reaction.

By using above mentioned procedure the determination of Pheniramine maleate has been achieved for 1-5 mg of pure sample of PM and in its pharmaceutical preparation (i.e Avil-25 mg tablet and injection Avil-10 ml)) but for convenience, the results as recorded in Table-1 has been considered only for 1,3 and 5 mg of sample size.

For the justification and validation of the proposed method recovery experiment were carried out by using standard drug addition method(Table-2). In this experiment a known amount of the pure compound is taken and to this, varying amounts of the pharmaceutical preparations of the same compounds are added. Finally the total amount of sample was calculated by expression:

$$\% \text{ Recovery} = N(\sum PQ - (\sum P)(\sum Q) \times 100 / N(\sum P^2) - (\sum P)^2$$

Where
$N = \sum N$ = Total number of observations, P = Amount of drug added, Q = Amount of drug obtained by calculation, $\sum P = \sum NP$, $\sum Q = \sum NQ$, $\sum PQ = \sum (NP)(Q)$, $\sum P^2 = \sum (NP)(P)$.

RESULTS AND DISCUSSION

The results as recorded in Table-1 were carried out for PM aliquots of 1 ml to 5ml but for convenience only 1,3 and 5 mg has been shown. All sample sizes of PM always establish stoichiometric ratio for PM: PFC to be 1:1. This stoichiometric ratio is similar for both i.e for pure PM sample and for pharmaceutical preparations i.e. in Avil-25 mg tablet and Avil-10 ml injection. This stoichiometric ratio 1:1 remains constant for PM: PFC even under varying reaction conditions i.e in varying reaction time, concentration of the reagent, reaction temperature and reaction medium etc. It has been also observed that 0.03N concentration of PFC and reaction duration of 15 minute at room temperature is most appropriate condition for the determination of PM drug. The effect of reaction medium has also been studied and has been observed that in absence of sulphuric acid the reaction proceeds very slow and concentration of 5N sulphuric acid gives accurate results. Method validation of proposed method was carried out by recovery experiment and calculation. The recovery of drug calculated for this has been found to be 99.55%. The results for recovery experiment were recorded in Table-2.

Table 1. DETERMINATION OF PHENIRAMINE MALEATE (PM) WITH 0.03N PFC

S. N	Amount of aliquots taken	Amount Present[#]	Reaction time	Molecularity	Amount obtained by calculation [##]	Error	SD	CV
	(ml)	(mg)	(min)		(mg)	(%)	(mg)	(mg)
Pheniramine maleate (PM) in Pure form								
1	1	0.998	15	1	0.991	− 0.70	0.0052	0.5247
2	3	2.991	15	1	2.973	− 0.60	0.0031	0.1043
3	5	4.986	15	1	4.963	− 0.46	0.0029	0.0584
Pheniramine maleate in Avil-25 mg tablet (Manufactured by Sanofi India Ltd)								
1	1	0.977	15	1	0.968	− 0.92	0.0028	0.2893
2	3	2.930	15	1	2.906	− 0.82	0.0022	0.0757
3	5	4.885	15	1	4.856	− 0.59	0.0010	0.0206
Pheniramine maleate in Avil-10 ml injection (Manufactured by Sanofi India Ltd)								
1	1	0.988	15	1	0.977	− 1.11	0.0031	0.3173
2	3	2.963	15	1	2.940	− 0.78	0.0026	0.0884
3	5	4.941	15	1	4.918	− 0.47	0.0033	0.0671

Mean value of three determinations has been done for each case.
Value obtained is the average of nine determination.

Table 2. RESULTS OF RECOVERY STUDIES BY STANDARD ADDITION

S N	Number of observations N	Amount of pure PM Present (mg)	Amount of PM added (injection) (mg) **P**	Total amount of drug obtained by calculation (mg)	Amount of drug obtained by calculation (mg)**Q**	**PQ**	**P^2**	Recovery %
1	3	0.998	0.988	1.976	0.978	0.966	0.976	99.55
2	3	0.998	1.977	2.961	1.963	3.881	3.909	
3	3	0.998	2.963	3.942	2.945	8.726	8.779	
4	3	0.998	3.952	4.927	3.932	15.539	15.618	
5	3	0.998	4.941	5.910	4.924	24.329	24.413	
	15		14.821		14.742	53.441	53.695	
	∑N		**∑P**		**∑Q**	**∑PQ**	**$\sum P^2$**	

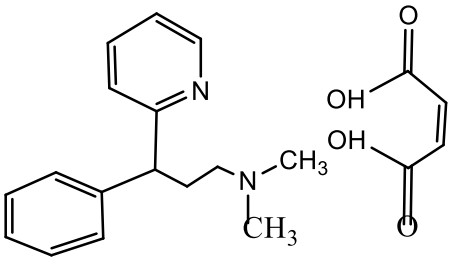

Figure 1. Chemical structure of Pheniramine maleate

CONCLUSION

The technique i.e visual volumetric technique is simple, rapid, accurate and precise and most economical analytical method was developed and validated. The selected method is suitable for routine analysis of Pheniarmine maleate in bulk drugs as well as formulations for pharmaceutical laboratories as this method does not involve any sophisticated instruments and are easily procurable at very low expenses. Thus accuracy, reproducibility, simplicity and cost-effectiveness of this method suggest its application in the quality control laboratories where the modern and expensive instruments are not available.

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