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Research Article

MICRO DETERMINATION OF PROMETHAZINE HYDROCHLORIDE DRUGS IN PURE FORM AND IN THEIR PHARMACEUTICAL PREPARATION WITH PYRIDINIUM FLUOROCHROMATE (PFC) REAGENT

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ABSTRACT

A simple visual titrimetric method have been described for the determination of Promethazine hydrochloride (PMH) in pure form and in its dosage forms.The principle of this method involves the oxidation of sulphur atom present in the Promethazine hydrochloride (PMH) to its corresponding sulphone compound by a known excess of potassium iodate in sulphuric acid medium followed by iodometric titration in presence of reagent pyridinium fluoro chromate (PFC). The stoichiometric ratio between the drug Promethazine hydrochloride (PMH) and Pyridinium fluorochromate has been found to be 1:1. The value of percentage error, coefficient of variation (CV) and standard deviation (SD) have been calculated for accuracy and precision of result.

Keywords: Promethazine hydrochloride drugs, Pharmaceuticals and titration.

INTRODUCTION

Promethazine hydrochloride (fig. 1) is chemically known as N,N-dimethyl-1-phenothiazin-10-ylpropan-2-amine hydrochloride having molecular formula $C_{17}H_{20}N_2S.HCl$. The drug Promethazine hydrochloride (PMH) is a phenothiazine based anti-histamine drug, was first synthesized by M. Nakanishi *et. al*[1] by employing 10-(-2-propyl)-phenothiazine in methanol, mercury (II)-sulphate, Me_2NH-dioxane in sulphuric acid and Raney nickel. This drug have excellent antihistaminic properties. Besides its antihistaminic action, it is potent antiemetic, anticholingeric and sedating agent, and significantly potentiates the action of analgesic and sedative drugs. This is also an important tranquilizer, antiallergic and H_1 receptor antagonist. Due to all such properties this drug is used to treat allergy symptoms like runny nose, sneezing, itching, itchy or watery eyes, conjuctivitis, hives and itchy skin rashes.It is also used in form of sedative and sleeping pills beside this it also prevents motion sickness, and treats vomiting and nausea or pain after surgery. Several workers have reported about the determination of Promethazine hydrochloride (PMH). The researcher's Clair *et al.*[2] have determined Promethazine hydrochloride by using perchloric acid as an oxidising reagent by visual titration method. Their experiment involves extraction of antihistamine product from tablets and capsules by employing solvent chloroform and thereafter titration with perchloric acid by adding acetic acid or acetonitrile in presence of suitable indicator. They observed that, drug Promethazine hydrochloride (PMH) establishes 1:1 stoichiometric ratio with oxidising reagent perchloric acid($HClO_4$).In another experiment Chauhan *et al.*[3] by employing iodometric visual titration method determined Promethazine hydrochloride by using N-bromosaccharin (NBS) as oxidizing reagent. They discovered that N-bromosaccharin (NBS) establishes 4:1 stoichiometric ratio with Promethazine hydrochloride. By using Chloramine-T as oxidising reagent Basavaiah and manjunathaswamy[4] introduced indirect titrimetric for the assay determination of

phenothiazine based antihistamine drugs. They in their method oxidised these drugs by using suphuric acid medium by a known excess of chloramine-T followed by the determination of unreacted oxidant iodometrically. Researcher's M.B. Devani *et al.*[5] by using double beam Beckman Model 25 spectrophotometer oxidised N-methyl group of promethazine hydrochloride to formaldehyde by employing potassium permanganate as oxidising reagent. An extractive spectrophotometric methods have been developed by Dilip B. Patil *et al.*[6] for the determination of promethazine hydrochloride (PMH) in tablet forms. Meakin *et al.*[7] introduced a Thin layer and Gas- liquid chromatographic technique for the assay determination of Promethazine hydrochloride in aqueous solutions. Column chromatography has been used by Albert R. Sperling[8] for the determination of Promethazine hydrochloride (PMH) in syrups. Gas-liquid chromatographic technique has been described by S. Stavchansky *et al.*[9] for the determination of Promethazine hydrochloride (PMH) in cocoa-butter white wax suppositories. The official method proposed for the assay determination of Promethazine hydrochloride (PMH) has been mentioned in British Pharmacopoeia[10] and United state Pharmacopoeia[11].

It has been observed from the survey of different literature, that no any researcher have used Pyridinium fluorochromate as an oxidising reagent for the determination of Promethazine hydrochloride by using simple visual volmetric tirtration method. In this paper simple, accurate and precise visual titrimetric volumetric method have been presented for the determination of Promethazine hydrochloride (PMH) in pharmaceuticals. In this paper we have selected Pyridinium fluoro chromate (PFC) as an oxidising reagent due to its low cost, easy preparation, high solubility and yield, less toxicity and short reaction duration with the drug Promethazine hydrochloride (PMH).

MATERIALS AND METHODS

Apparatus

Calibrated Burette, Graduated Pipette, Measuring cylinders, Iodine flask (Stoppered flask) etc. were used to carry out volumetric titration successfully.

MATERIALS

All chemicals used in an analysis were of analytical reagent grade and double distilled water was used throughout the experiment. A pure pharmaceutical grade Promethazine hydrochloride on request has been supplied by Akums Drugs and Pharmaceuticals Ltd, 304, Mohan Place, L.S.C., Block-C, Saraswati Vihar, New Delhi, India as gift sample whereas tablet Phanergan-10 mg and Injection Phenergan -2 ml (Manufactured by Akums Drugs and Pharmaceuticals Ltd, Ranipur, Haridwar, Uttarakhand, India) has been purchased from commercial sources in the local market.

REAGENTS AND SOLUTIONS

Solution of Pyridinium Fluorochromate (0.03 N)

Solution of PFC 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.

Solution of Sodium thio sulphate (0.01 N)

Stock solution of sodium thio sulphate(0.01N) 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. The stock solution prepared in this way was standardised by using 0.01 N potassium dichromate (Moly Chem) solution iodometrically by using starch as an indicator.

Solution of Potassium Dichromate (0.01 N)

Stock solution of $K_2Cr_2O_7$ 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.

Potassium Iodide (10%)

10% W/V aqueous solution was prepared in distilled water. The Potassium iodide used for an experiment is of AR grade of RANKEM.

Starch Solution (1%)

1% of W/V aqueous solution of starch (LOBA Chemie) was prepared in boiling distilled water. The paste formed this way was filtered and kept to cool for some minutes. Always fresh starch solution has been prepared for accurate results.

Preparation of solutions

Preparation of Pure Sample Solution

Taken 100 mg pure compound of Promethazine hydrochloride (CPH) supplied on request, as gift sample by Akums Drugs and Pharmaceuticals Ltd, 304, Mohan Place, L.S.C., Block-C, Saraswati Vihar, New Delhi,India, in 100 ml volumetric flask and first dissolved it in minimum quantatity 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 upto the mark with distilled water.

Preparation of tablet Solution

The 20 Phenergan-10mg tablets manufactured by Akums Drugs and Pharmaceuticals Ltd, Ranipur, Haridwar, Uttarakhand, 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 PMH.

Preparation of injection solution

The contents of 20 ampoules Phenergan- 2 ml injection manufactured by Akums Drugs and Pharmaceuticals Ltd, Ranipur, Haridwar, Uttarakhand, India were mixed properly and volume of injection equivalent to 100 mg of the pure sample were taken and diluted upto the mark with distilled water in 100 ml calibrated flask, so that concentartion 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. Again 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 evaluate the authenticity of the method. The expression used to determine the amount of drug present in the measured aliquot for each experiment is as follows:

Weight (mg) of sample =

$$\frac{M \, X N \, (B - S) \ldots\ldots (1)}{n}$$

Where,
M = Molecular weight of the sample.
N = Normality of sodium thiosulphate solution.
B = Volume of sodium thiosulphate solution for blank.
S = Volume of sodium thiosulphate solution for sample.
n = Stoichiometry of the reaction.
For the justification and validation of the proposed method recovery experiment were carried out by using standard drug addition method.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. The total amount of sample was calculated by expression:

% Recovery=

$$\frac{N \, (\sum XY - (\sum X) \, (\sum Y) \, X \, 100 \ldots (2)}{N \, (\sum X^2) - (\sum X)^2}$$

Where,
N= $\sum N$ = Total number of observations, X = Amount of drug added. Y = Amount of drug obtained by calculation.
$\sum X = \sum NX$, $\sum Y = \sum NY$,
$\sum XY = \sum (NX) (Y)$,
$\sum X^2 = \sum (NX) (X)$

RESULTS AND DISCUSSION

Possible course of reaction

The selected drug Promethazine hydrochloride (PMH) belongs to phenothiazine class and its structure consists of tricyclic ring system in which two aromatic rings are linked by branched alkyl chain,sulphur atom and terminal nitrogen atom(fig.1).In other word we can say that sulphur atom present between two aryl rings is the bridging entity between the two aryl rings.The nitrogen atom present in the drug PMH are not of the basic nature.Hence the oxidising reagent PFC oxidises the sulphur atom present between the two aryl ring to corresponding sulphone but not nitrogen atom as they are not of basic nature.Thus sulphur atom of the drug PMH during oxidation reaction with oxidising reagent PFC consumes one

equivalent of PFC per mole and forms sulphoxide and due to this PMH with PFC establishes stiochiometric ratio of 1:1.This reaction between drug PMH and PFC takes ten minutes for its completion.On the basis of stiochiometric ratio established between PFC and pharmaceutical drug Promethazine hydrochloride (PMH) and after the survey of different literature, the scheme for proposed reaction is expressed in (fig. 2).

By using above mentioned process the determination of Promethazine hydrochloride has been achieved for 1-5 mg of pure sample of PMH and in its pharmaceutical preparation (i.e PHENERGAN tablet and injection) but for convenience, the results as recorded in Table-1 have been shown only for 1,3 and 5 mg of sample size. It has been observed from the different results obtained by the above analysis that, the drug Promethazine hydrochloride (PMH) in pure form and in its different pharmaceutical preparations i.e . in Pherergan tablet and in Phenergan injection with reagent Pyridinium fluoro chromate (PFC) establishes 1:1 ratio between Drug:PFC. It has also been observed that, this stoichiometric ratio is similar for both i.e for pure PMH sample and for pharmaceutical preparations i.e. in Pherergan tablet and injection. The results obtained were recorded in table -1.This stoichiometric ratio 1:1 remains constant for PMH: PFC even under varying reaction conditions i.e in varying reaction time, concentration of the reagent, reaction temperature and reaction medium etc. Reaction takes 10 minutes for the completion of reaction. Reaction time below ten minute gives inaccurate results due to the incompletion of the reaction whereas increase in reaction time above ten minutes does not changes the percentage recovery of the sample but it remains constant throughout the reaction after 10 minutes.Sulphuric acid has been selected as reaction medium for this determiantion its 10ml of 5N sulphuric acid is recommended as suitable reaction medium for the said reaction.It has also been observed that reaction proceed fast and gives appropriate results at normal room temperature i.e. between 25^{0}C to 30 ^{0}C.

Method validation-Recovery experiment

For analysing the accuracy and reliability of the methods recovery experiment has been carried out.The recovery calculated for this has been found to be 99.51%.The results for recovery experiment were recorded in Table-2.

CONCLUSION

The stoichiometric ratio between the PFC reagent and Promethazine hydrochloride (PMH) has been found to be 1:1.This ratio remains constant even under varying reaction conditions i.e. change in concentration of the reagent, reaction time, reaction medium etc.It has been also observed that 0.03N concentration of PFC and reaction duartion of 10 minute at room temperature is most appropriate condition for the determination of PMH drug.The effect of reaction medium has also been studied and observed that in absence of sulphuric acid the reaction proceed very slow and conentration of 5N sulphuric acid gives accurate results.This visual volumetric titration method is simple,rapid, accurate and economically best in comprasion to other method where sophisticated instruments is required.The proposed method is convenient to be carried out at any laboratory.Thus proposed method is best for routine quality analysis of Promethazine hydrochloride in pure form and in its pharmaceutical preparations for pharmaceutical companies manufacturing the PMH drug.

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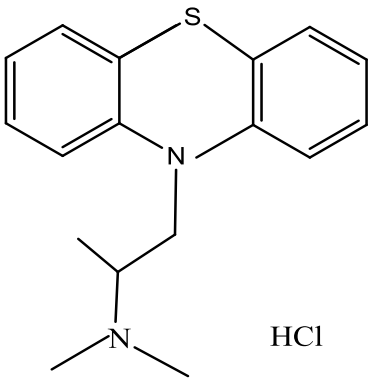
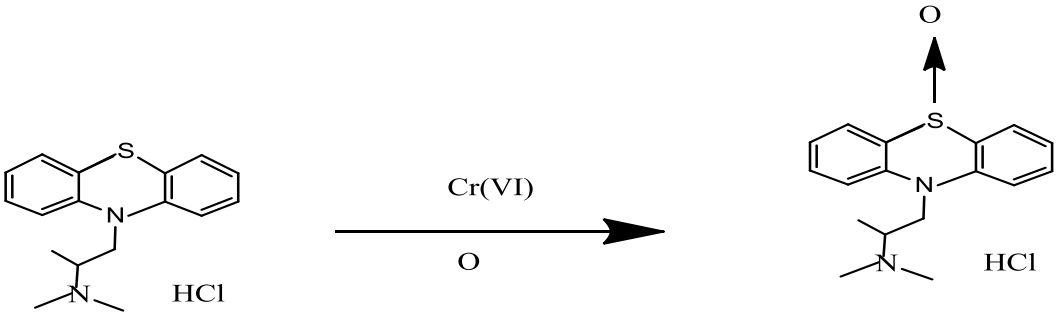


Fig. 1: Chemical structure of Promethazine hydrochloride



Promethazine Hydrochloride **Oxidised product**

Fig. 2: Scheme for possible reaction path

Table 1: Determination of Promethazine hydrochloride (PMH) with 0.03N PFC

S.No	Amount of aliquots taken	Amount Present#	Reaction time	Molecularity	Amount obtained by calculation ##	Error	SD	CV
	(ml)	(mg)	(min)		(mg)	(%)	(mg)	(mg)
Promethazine hydrochloride (PMH) in Pure form								
1	1	0.996	10	1	0.987	– 0.90	0.0026	0.2634
2	3	2.985	10	1	2.962	– 0.77	0.0028	0.0945
3	5	4.975	10	1	4.945	– 0.60	0.0035	0.0708
Promethazine hydrochloride in form of Phenergan tablet (Manufactured by Akums Drugs Ltd)								
1	1	0.969	10	1	0.961	– 0.83	0.0025	0.0025
2	3	2.906	10	1	2.886	– 0.69	0.0032	0.0032
3	5	4.843	10	1	4.816	– 0.56	0.0024	0.0024
Promethazine hydrochloride in form of Phenergan injection (Manufactured by Akums Drugs Ltd)								
1	1	0.976	10	1	0.967	– 0.92	0.0020	0.2068
2	3	2.928	10	1	2.905	– 0.79	0.0017	0.0585
3	5	4.880	10	1	4.852	– 0.57	0.0009	0.0185

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 method

S.No	Number of observations	Amount of pure PMH Present	Amount of PMH added (present in injection)	Total amount of drug obtained by calculation	Amount of drug obtained by calculation	XY	X^2	Recovery
	N	(mg)	(mg) X	(mg)	(mg) Y			%
1	3	0.996	0.972	1.960	0.964	0.937	0.945	99.51
2	3	0.996	1.945	2.927	1.931	3.756	3.783	
3	3	0.996	2.917	3.894	2.898	8.453	8.509	
4	3	0.996	3.889	4.865	3.870	15.050	15.124	
5	3	0.996	4.862	5.831	4.842	23.542	23.639	
	15		14.585		14.505	51.738	52.000	
	∑N		∑X		∑Y	∑XY	$\sum X^2$	

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