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TITRIMETRIC ASSAY OF SOME ANTIHISTAMINES WITH PYRIDINIUM FLUORO CHROMATE (PFC) REAGENT

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ABSTRACT

In the present paper, simple, convenient accurate, precise and cost effective titrimetric (Visual volumetric) method has been reported for the estimation of some antihistamine drugs e.g. Cyproheptadine hydrochloride (CPH), Fexofenadine hydrochloride (FFH), Promethazine hydrochloride (PMH) and Pheniramine maleate (PM) in pure form and in their pharmaceutical preparations such as Ciplactin (Tab), Allegra (Tab), Phenergan (Tab and Inj) and Avil (Tab and Inj) with Pyridinium fluoro chromate (PFC) reagent. The principle of this method is based on the fact, that each pharmaceutical drug consists of certain organic functional group which on oxidation by a known excess of potassium iodate in sulphuric acid medium followed by iodometric titration in presence of reagent Pyridinium fluoro chromate (PFC) establishes stoichiometric relationship between drug molecule and an oxidising reagent Pyridinium fluoro chromate (PFC).Different results obtained for each drug during experiment, has been validated by different statistical parameters such as percentage error, standard deviation (SD) and coefficient of variation (CV).Results obtained from these statistical parameters proves the accuracy and precision of adopted method.

Keywords: Titrimetric determination, antihistamine drugs, Pyridinium fluorchromate, iodometric titration.

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INTRODUCTION

The drug antihistamine [1-4] is used to neutralize the effects of histamine, or inhibits its production in body. These drugs are mainly used in the treatment of allergies caused due to allergens. Antihistamine drugs are mainly used to cure itching (pruritus), hives (urticaria), hay fever (seasonal allergic rhinitis), insect bites and stings. Antihistamine drugs are also used to reduce the feeling of sick (vomiting) and sick (nausea) beside this also in the treatment of anxiety and branchial asthma. .Here the selected drugs Cyproheptadine hydrochloride (CPH) , Promethazine hydrochloride (PMH) and Pheniramine maleate (PM) belongs to first generation whereas Fexofenadine hydrochloride (FFH) is of second generation antihistamines. The drug Cyproheptadine hydrochloride, is chemically known as 4-(5Hdibenzo [a,d]-cyclohepten-5-ylidene)-1-methylpiperidine hydrochloride (Fig.1), Fexofenadine hydrochloride as as (±)-4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-butyl]-α,α-dimethyl benzene acetic acid hydrochloride (Fig. 2), Promethazine hydrochloride as N,N-dimethyl-1-phenothiazin-10-ylpropan-2-amine hydrochloride (Fig.3) and Pheniarmine maleate is known as N, N- dimethyl – 3 –phenyl – 3 - (2-pyridyl) propylamine hydrogen maleate (Fig. 4).

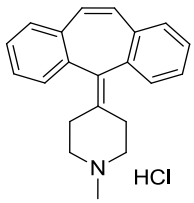

Figure 1: Cyproheptadine hydrochloride

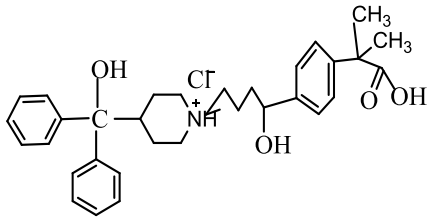

Figure 2: Fexofenadine hydrochloride

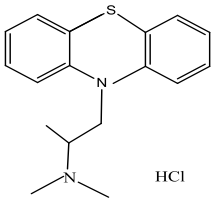

Figure 3: Promethazine hydrochloride

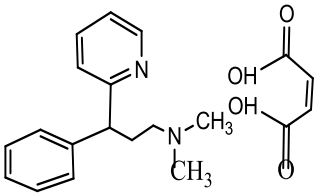

Figure 4: Pheniramine mlaeate

Different analytical techniques have been reported by different researches for the estimation of antihistamine drugs in their pure form and for their pharmaceutical formulations. The assay determination of drug Cyproheptadine (CPH) is officially listed in United States Pharmacoepia[5] by using perchloric acid as titrant in non-aqueous titration whereas UV spectrophotometer in Indian Pharmacopeia[6].Assay determination of Fexofenadine hydrochloride (FFH) has been mentioned by chromatographic technique in United States Pharmacopeia[7]. Determination of Promethazine hydrochloride (PMH) has been described in British Pharmacoepia[8] and United state Pharmacoepia[9].Similarly the official method for Pheniramine maleate (PM), by using reagent perchloric acid through non aqueous titration has been reported by British Pharmacopoeia[10] and United State Pharmacopeia[11].

After review of different literature it has been observed that different techniques such as Chromatographic, spectrophotometric etc have been reported by different researchers for the assay determination of these drugs. All of these techniques involves sophisticated instruments and has been proved that these instrumental methods are generally not as accurate and precise as the titrimetry in microanalysis. . On the other hand no any researcher up to till date, have employed Pyridinium fluoro chromate (PFC) as an oxidant for the estimation of these antihistamines i.e. Cyprohepatdine hydrochloride (CPH), Fexofenadine hydrochloride (FFH), Promethazine hydrochloride (PMH) and Pheniramine maleate (PM).This paper describes about , simple, accurate, precise, rapid and cost effective visual titrimetric technique (Volumetric titration technique) for the assay determination of these drugs in form pure and in their formulations in form of tablets and injections. This technique is very much useful to pharmaceutical companies for the quality control assessment of these drugs in their routine quality analysis.

MATERIALS AND METHODS

Materials

Double distilled water and all other chemicals used in an analysis were of analytical reagent grade and was used throughout the experiment. A pure pharmaceutical grade Cyproheptadine hydrochloride (CPH) supplied on request, as gift sample by CIPLA Ltd, Mumbai (India), Fexofenadine hydrochloride (FFH) and Pheniramine maleate (PM) by Sanofi India Ltd., Ankleshwar, Distt-Bharuch, Gujarat(India) whereas pure Promethazine hydrochloride 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 Ciplactin-4mg tablets (Manufactured by Cipla Ltd, Sigaddi, Kotdwar, Pauri Garhwal), Allegra-120 mg tablet (Manufactured by Sanofi India, Ltd, Ankleshwar, Distt-Bharuch, India), Phanergan-10 mg and Injection Phenergan -2 ml (Manufactured by Akums Drugs and Pharmaceuticals Ltd, Ranipur, Haridwar, Uttarakhand, India) and similarly tablet Avil-25 mg and an injection Avil-10ml (Manufactured by Sanofi India, Ltd, Ankleshwar, Distt-Bharuch,Gujarat, India) has been purchased from commercial sources in the local market.

Reagents and solutions

0.497 gm of PFC was accurately weighed and dissolved in 150 ml glacial acetic acid (MERCK) and made up the volume with distilled water in 250 ml volumetric flask. The solution was standardised iodometrically for preparing 0.03N PFC solution with standard Sodium thio sulphate solution using starch as an indicator.

A 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. The solution was standardised by using 0.01 N potassium dichromate (Moly Chem) solution iodometrically by using starch as an indicator for preparing 0.01N Sodium thio sulphate solution.

Preparation of sample Solution

100 mg pure sample of different antihistamine drugs i.e Cyproheptadine hydrochloride (CPH), Fexofenadine hydrochloride (FFH), Promethazine hydrochloride (PMH) and Pheniramine maleate (PM) supplied by different pharmaceutical companies as mentioned above was accurately weighed and dissolved in distilled water in a 100 mL volumetric flask and solution made up to the mark to obtain a concentration of 1mg/mL.

Preparation of tablet solution

Twenty tablets obtained from different local commercial source of each antihistamine drugs i.e. Ciplactin -4mg, Allegra-120mg, Phenergan-10mg and Avil 25mg were crushed to a fine powder and powder equivalent to 100 mg of sample was taken separately in 100 mL calibrated volumetric flask and dissolved in minimum amount of distilled water. After getting a homogenous solution the flask was made upto the mark with distilled water.

Preparation of Injection solution

The contents of 20 ampoules of each drug i.e. Phenergan- 2 ml injection and Avil- 10 ml purchased from local commercial source 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 concentration of flask become 1mg/ml.

Method[12,13]

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. For the 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.

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

$$\text{Weight (mg) of sample} = \frac{\text{Mw X N (Vb -Vs)}}{\text{n}} \ldots\ldots(1)$$

Where,
M_W = Molecular weight of the sample, N = Normality of sodium thio sulphate solution, V_b = Volume of sodium thio sulphate solution for blank, V_s = Volume of sodium thiosulphate solution for sample, n = Stoichiometry of the reaction.

By using above mentioned method the estimation of different antihistamine drugs has been achieved for 1-5 mg of pure sample of these drugs and in their pharmaceutical preparation(i.e Ciplactin, Allegra, Phenergan, Avil) but for convenience, the results as recorded in Table-1 have been shown only for 1,3 and 5 mg of sample size.

RESULTS AND DISCUSSIONS

It has been observed from result of Table-1 that, stoichiometric ratio between Pyridinium fluoro chromate (PFC) reagent and different antihistamine drugs under investigation i.e. Cyprohepatdine hydrochloride (CPH), Promethazine hydrochloride (PMH), Pheniarmine maleate (PM) establishes (1:1) ratio whereas Fexofenadine hydrochloride (FFH) establishes 1:2 ratio in pure form and in their pharmaceutical preparations. Similarly it has been found that reaction time required for the completion of oxidation reaction in case of Cyprohepatdine hydrochloride (CPH), Fexofenadine hydrochloride (FFH), Promethazine hydrochloride (PMH), is 10 minute, whereas for Pheniarmine maleate (PM) it has been observed as 15 minutes. It has been found that in case of reaction time lesser than as mentioned in Table-1 gives inaccurate results due to the incompletion of reaction. This estimation of antihistamine drugs does not require specific temperature and all reactions occur at room temperature. Here 5N sulphuric acid is used as reaction medium for this oxidation reaction. It has also been observed that when reaction was carried out in absence of sulphuric acid then it was slower, in comparison to the reaction that was carried out in presence of sulphuric acid and also percentage error in results were also has been increased. Thus it has been concluded that reaction medium is very necessary for accurate results. It has also been found that 5ml volume of 5N H_2SO_4 is the appropriate for the complete oxidation of all selected drugs under investigation.

CONCLUSION

The proposed 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 all the drugs i.e. Cyproheptadine hydrochloride (CPH), Fexofenadine hydrochloride (FFH) Promethazine hydrochloride (PMH) and Pheniramine maleate (PM) in bulk drugs as well as formulations for pharmaceutical laboratories as this method does not have any sophisticated instruments and is easily procurable at very low expenses. Thus due to 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.

Table 1: Estimation of antihistamine drugs in pure form and in their pharmaceutical preparation with 0.03N PFC reagent

Drug Sample	Aliquots taken	Amount present*	Reaction time	Molecularity	Amount obtained**	Error	SD	CV
	(ml)	(mg)	(min)		(mg)	%	(mg)	(mg)
1.Cyproheptadine	1	0.998	10	1	0.989	− 0.90	0.0057	0.5763
HCl (Pure)	3	2.992	10	1	2.969	− 0.77	0.0038	0.1280
Ciplactin	5	4.986	10	1	4.957	− 0.58	0.0032	0.0646
(Tab)	1	0.993	10	1	0.985	− 0.81	0.0022	0.2234
	3	2.975	10	1	2.956	− 0.64	0.0027	0.0913
	5	4.930	10	1	4.915	− 0.31	0.0037	0.0753
2.Fexofenadine	1	0.993	10	2	0.985	−0.81	0.0026	0.2639
HCl. (Pure)	3	2.979	10	2	2.958	−0.70	0.0018	0.0608
Allegra	5	4.965	10	2	4.938	−0.54	0.0009	0.0182
(Tab)	1	0.989	10	2	0.982	−0.71	0.0029	0.2953
	3	2.955	10	2	2.938	−0.58	0.0016	0.0545
	5	4.927	10	2	4.905	−0.45	0.0011	0.0224
3.Promethazine	1	0.996	10	1	0.987	− 0.90	0.0026	0.2634
HCl (Pure)	3	2.985	10	1	2.962	− 0.77	0.0028	0.0945
Phenergan	5	4.975	10	1	4.945	− 0.60	0.0035	0.0708
(Tab)	1	0.969	10	1	0.961	− 0.83	0.0025	0.2601
Phenergan	3	2.906	10	1	2.886	− 0.69	0.0032	0.1109
(Injection)	5	4.843	10	1	4.816	− 0.56	0.0024	0.0498
	1	0.976	10	1	0.967	− 0.92	0.0020	0.2068
	3	2.928	10	1	2.905	− 0.79	0.0017	0.0585
	5	4.880	10	1	4.852	− 0.57	0.0009	0.0185
4. Pheniramine	1	0.998	15	1	0.991	− 0.70	0.0052	0.5247
Maleate (Pure)	3	2.991	15	1	2.973	− 0.60	0.0031	0.1043
Avil	5	4.986	15	1	4.963	− 0.46	0.0029	0.0584
(Tab)	1	0.977	15	1	0.968	−0.92	0.0028	0.2893
Avil	3	2.930	15	1	2.906	−0.82	0.0022	0.0757
(Injection)	5	4.885	15	1	4.856	−0.59	0.0010	0.0206
	1	0.988	15	1	0.977	−1.11	0.0031	0.3173
	3	2.963	15	1	2.940	−0.78	0.0026	0.0884
	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 determinations.

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