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Oxidative Determination of Some New Antihistamine Drugs in Pure Form and in Their Pharmaceutical Preparations by Using Cu (III) Reagent

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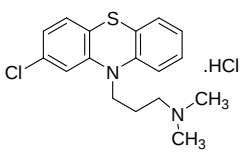
Abstract— In the present work a simple and convenient titrimetric method has been described for the determination of some Antihistamine Drugsin pure form and in their pharmaceutical preparations i.e. Chlorpromazine, Prochloroperazine Maleate, Promethazine, Triflupromazine and TrifluoparazineusingPotassiumdipertelluratocuprate (III) as an oxidizing reagent. This reagent has widely been used for the determination of several other pharmaceutical products. Aliquots containing 1-5 mg of the sample were taken in 100 mL stoppered conical flask, 5 ml of 0.035 N Potassiumdipertelluratocuprate (III) and 10 ml of 5 N H_2SO_4 was added to it. The reaction mixture was shaken thoroughly and allowed to react for required reaction time (5-15 min) at room temperature (25-30^{0}C). After the reaction was over 5 ml of 10% KI solution was added to it. Contents shaken thoroughly and allowed to stand for a minute. The liberated iodine was titrated with 0.01 N sodium thiosulphate using starch as indicator. During estimation it was noted that the excipients present in pharmaceutical preparations do not interfere. The value of percentage error, standard deviation (SD) and coefficient of variation prove the method to be precise and reproducible. To establish authenticity of the method, recovery experiments were also carried out by standard drug addition method.

Keywords— Antihistamine drugs, potassiumdipertelluratocuprate (III) reagent, titration, standard deviation.

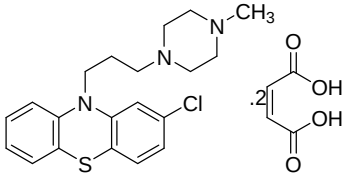
I. INTRODUCTION

A chemical found in some of the body's cells - causes many of the symptoms of allergies [1-5], such as a runny nose or sneezing. When a person is allergic to a particular substance, such as a food or dust, the immune system mistakenly believes that this usually harmless substance is actually harmful to the body [6-8]. In an attempt to protect the body, the immune system starts a chain reaction that prompts some of the body's cells to release histamine [9-15] and other chemicals into the bloodstream. The histamine then acts on a person's eyes, nose, throat, lungs, skin, or gastrointestinal tract, causing allergy symptoms [16-18]. In such case antihistamine medication helps to fight symptoms of allergy.

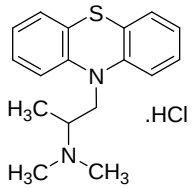
The certain compounds or medicines that neutralize or inhibit the effect of histamine in the body, used chiefly in the treatment of allergic disorders and colds or the drugs that relieve cold or allergy symptoms by blocking the action of histamine or The drugs used to counteract the physiological effects of histamine are called Antihistamine drugs. The structures of some phenothiazine drugs used are as follow



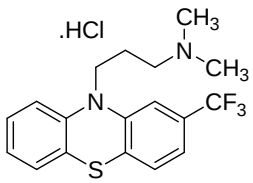
Chloropromazine hydrochloride



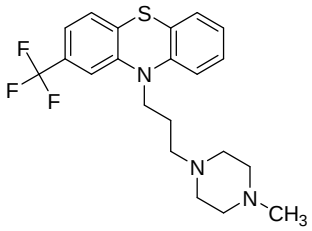
Prochlorperazine Maleate



Promethazine Hydrochloride



Triflupromazine Hydrochloride



Trifluoperazine

Because of the great medicinal value, their estimation has widely been studied. Most of the methods used for the determination of Antihistamine drugs involve sophisticated instruments and complicated techniques. In the present paper a new simple titrimetric method has been described for the determination of Antihistamine drugs with Cu (III) reagent. In Indianpharmacopoeia (IP) 2007, vol. 3, the determination of Prochlorperazine, Promethazine Hydrochloride, Trifluoperazine and Triflupromazine tablets are given by Infrared Absorption Spectroscopy (page 1598, 1603, 1828 and1830), While for Chlorpromazine hydrochloride drug is given in Indian pharmacopoeia (IP) 2007, vol. 2, determination by Infrared Absorption Spectroscopy.

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II. EXPERIMENTAL

Experimental work is divided in to 4 part i.e. Synthesis of reagent, Solution preparation, General procedure and Calculation. Whole experimental work is described as follow-

A. *Synthesis / Reagents and solutions*

Potassiumdipertelluratocuprate (III) reagent (12-13) $K_5H_4[Cu(TeO_6)_2]$. $18H_2O$(0.035 M) was prepared by adding copper sulphate (Merck) (7.0805 g), potassium tellurite (CDH) (15.8630 g), potassium persulphate (Loba-Chemie) (21.1010 g), potassium hydroxide (Merck) (40 g), to 400 mL of distilled water [19]. The mixture was shaken thoroughly and boiled on hot plate for about 20 minutes. When the boiled mixture turned intensely red, the boiling was continued for another 20 minutes. The mixture was then cooled at room temperature, filtered through cintered glass crucible (G-4) and diluted to 500 mL with distilled water. If an excess of persulphate was present boiling for longer time is required for its complete decomposition (Test for presence of persulphate in prepared solution: Acidify 1 mL solution with dilute H_2SO_4 till no red Colour appeared thus Cu (III) converted to Cu (II). Add 5 mL of 0.5 M $NaHCO_3$ and 2 mL of 5% potassium iodide solution. Allowed it to stand for 2 minutes and then added two drops of starch solution. A blue color indicates the presence of persulphate.). The alkaline solution of Cu (III) prepared in this way was fairly stable and the concentration remains practically unaltered for several months.

B. *Standardization of Cu (III) Reagent*

Aliquots (5 mL) of the solution were treated with 5 mL of 0.02 M standardized arsenite solution. The mixture was allowed to stand for 3-4 min then acidified with 0.5 M H_2SO_4 till a green suspension disappeared and a clear solution was obtained. This solution was treated with 5 mL of 0.5 M $NaCO_3$ and back titrated the unconsumed arsenite with standard iodine solution (0.01 N) using starch as an indicator [20]. A blank was also run.

Stock solution (Aqueous) of sodiumthiosulphate (0.01N) (Merk)was prepared and standardized by (Merk) 0.01 N potassium dichromate solution iodometrically. Aqueous solution of potassium iodide (Baker analyzed reagent) and (10% w/v) starch were also prepared.

C. *Sample Solution*

Accurately weighed (100 mg) pure sample of Chlorpromazine hydrochloride, Prochlorperazine, Promethazine Hydrochloride, Trifluoperazine and Triflupromazine were dissolved in distilled water in a 100 mL volumetric flask and solution made up to the mark to give a concentration of 1 mg/mL .

D. *Tablets Solution*

Twenty tablets of pharmaceutical products were crushed to a fine powder and powder equivalent to 100 mg of sample was taken in 100 mL calibrated volumetric flask and dissolved in minimum amount of distilled water. After getting a clear solution the flask was made upto the mark with distilled water.

E. *General Process*

Aliquots containing 1-5 mg of the sample were taken in 100 mL stoppered conical flask and 5 mL of 0.035 M Cu (III) reagent and 10 mL of 5 N H_2SO_4 was added to it. The reaction mixture was shaken thoroughly and allowed to react for required reaction time (5-15 minutes) at room temperature (25-30^{0}C). After the reaction was over, 5 mL of 10% potassium iodide was added to it and titrated against standardized sodium thiosulphate solution (0.01 N) using starch indicator. A blank experiment was also performed under identical conditions using all the reagents except the sample. The amount of the sample was calculated by the following expression.

F. *Calculation*

$$\text{Weight of sample(mg)} = \frac{\text{M} \times \text{N(B} - \text{S)}}{\text{n}}$$

Where, M = Molecular weight of the sample,
N = Normality of sodiumthiosulphate solution,
B = Volume of sodiumthiosulphate solution for blank,
S = Volume of sodiumthiosulphate solution for sample,
n = Stoichiometry of the reaction.

$$\% \text{ Error} = \frac{(Xa - Xb)}{Xb} \times 100$$

Where, Xa = Mean of obtain value and Xb = Mean of true value.

Standard Deviation

$$SD = \sqrt{\frac{(X_1 - \bar{X})^2 + (X_2 - \bar{X})^2 - \text{----------} - (X_n - \bar{X})^2}{(n-1)}}$$

Where,
$\bar{X}$ = Average value of amount obtained by calculations.
X_1, X_2, ----------X_n = Amount obtained by calculations in different observations.
n= Number of observations.

Coefficient of Variation (CV)

$$CV = \frac{SD \times 100}{\bar{X}}$$

Where,
SD =Standard Deviation $\bar{X}$ = Average value of the amount obtained by calculations.
Recovery experiment

$$\% \text{ Recovery} = \frac{N(\sum XY) - (\sum X)(\sum Y)}{N(\sum X^2) - (\sum X)^2} \times 100$$

Where,
N = Σ N = Total number of observations, X = Amount of drug added.
Y = Amount of drug obtained by calculation, ΣX = Σ NX

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TABLE I. Milligram determination of some antihistamine agents in pure form and in their pharmaceutical preparations with (0.035N) Cu(III) reagent in acidic medium.

Sample	Aliquots Taken (ml)	Amt. Present* (mg)	Reaction Time (min.)	Molecularity (n)	Amt. Obt. by Cal.	Error (%)	Sd	Cv
Chlorpromazine(Pure)	1	0.994	10	4	0.989	0.50	0.0030	0.3033
	3	2.982	10	4	2.978	0.13	0.0027	0.0907
	5	4.970	10	4	4.967	0.06	0.0032	0.0644
Clozine(Tab.)	1	0.946	10	4	0.940	0.63	0.0032	0.3404
	3	2.838	10	4	2.825	0.46	0.0044	0.1558
	5	4.730	10	4	4.726	0.08	0.0025	0.0529
Chlorpromazin	1	0.968	10	4	0.961	0.72	0.0025	0.2601
	3	2.904	10	4	2.890	0.48	0.0049	0.1696
	5	4.840	10	4	4.830	0.21	0.0058	0.1201
Prochloroperazi-ne Maleate (Pure)	1	0.998	10	4	0.988	1.00	0.0040	0.4049
	3	2.994	10	4	2.983	0.37	0.0070	0.2347
	5	4.990	10	4	4.980	0.20	0.0066	0.1325
Buccal(Tab.)	1	0.980	10	4	0.973	0.71	0.0035	0.3597
	3	2.940	10	4	2.931	0.31	0.0066	0.2252
	5	4.900	10	4	4.893	0.14	0.0032	0.0654
Buccastem M (Tab.)	1	0.986	10	4	0.980	0.61	0.0031	0.3163
	3	2.958	10	4	2.948	0.34	0.0040	0.1357
	5	4.930	10	4	4.928	0.04	0.0031	0.0629
Promethazine (Pure)	1	0.998	10	4	0.980	1.20	0.0031	0.3144
	3	2.994	10	4	2.981	0.43	0.0035	0.1174
	5	4.990	10	4	4.979	0.22	0.0042	0.0844
Avomine(Tab.)	1	0.976	10	4	0.970	0.61	0.0045	0.4639
	3	2.928	10	4	2.920	0.27	0.0040	0.1370
	5	4.880	10	4	4.873	0.14	0.0037	0.0759
Emispan (Tab.)	1	0.974	10	4	0.964	1.03	0.0037	0.3838
	3	2.922	10	4	2.914	0.27	0.0042	0.1441
	5	4.870	10	4	4.863	0.14	0.0040	0.0823
Triflupromazine (Pure)	1	0.998	10	2	0.985	1.30	0.0053	0.5381
	3	2.994	10	2	2.979	0.50	0.0053	0.1779
	5	4.990	10	2	4.978	0.24	0.0053	0.1065
Corzine(Tab.)	1	0.982	10	2	0.973	0.92	0.0053	0.5447
	3	2.946	10	2	2.930	0.54	0.0051	0.1741
	5	4.910	10	2	4.894	0.33	0.0051	0.1042
Gencalm(Tab.)	1	1.024	10	2	1.009	1.46	0.0053	0.5253
	3	3.072	10	2	3.019	1.73	0.0049	0.1623
	5	5.120	10	2	5.061	1.15	0.0053	0.1047
Trifluoparazine (Pure)	1	0.994	15	4	0.983	1.11	0.0062	0.6307
	3	2.982	15	4	2.967	0.50	0.0101	0.3404
	5	4.970	15	4	4.953	0.34	0.0070	0.1413
Corzine(Tab.)	1	0.986	15	4	0.974	1.22	0.0047	0.4825
	3	2.958	15	4	2.946	0.41	0.0044	0.1494
	5	4.930	15	4	4.918	0.24	0.0044	0.0895
Espazine(Tab.)	1	0.978	15	4	0.969	0.92	0.0057	0.5882
	3	2.934	15	4	2.919	0.51	0.0047	0.1610
	5	2.934	15	4	2.919	0.51	0.0047	0.1610

Tab. = Tablet, **Inj.** = Injection.
***In each sample nine determinations were done
****** Average of nine determinations

TABLE II. Recovery studies of chlorpromazine by standard drug addition method.

No. of Ob (n)	Amt. Present (pure) (mg)	Amt. of Drug Added (mg) X	Total Amt. of Drug Obt. by Cal. (mg)	Amount of Drug Obt. by Cal. (mg) Y	XY	X2	Recovery (%)
3	0.994	0.946	1.929	0.940	0.889	0.895	99.93
3	0.994	1.892	2.869	1.980	3.746	3.580	
3	0.994	2.838	3.809	2.820	8.003	8.054	
3	0.994	3.784	4.749	3.760	14.228	14.319	
∑N=12		∑X=9.460		∑Y= 9.500	∑XY= 26.866	∑X2= 26.848	

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TABLE III. Recovery studies of prochloroperazine maleateby standard drug addition method.

No. of Ob (n)	Amt. Present (pure) (mg)	Amt. of Drug Added (mg) X	Total Amt. of Drug Obt. by Cal. (mg)	Amount of Drug Obt. by Cal. (mg) Y	XY	X^2	Recovery (%)
3	0.998	0.980	1.961	0.973	0.954	0.960	99.18
3	0.998	1.960	2.934	1.926	3.775	3.842	
3	0.998	2.940	3.907	2.919	8.582	8.644	
3	0.998	3.920	4.880	3.892	15.257	15.366	
∑N=12		∑X=9.800		∑Y= 9.710	∑XY= 28.568	$\sum X^2$= 28.812	

TABLE IV. Recovery studies of promethazine by standard drug addition method.

Number of Observation (N)	Amount Present (Pure) (mg)	Amount of Drug Added (mg) X	Total Amount of Drug Obtained by Calculation (mg)	Amount of Drug Obtained by Calculation (mg) Y	XY	X^2	Recovery (%)
3	0.998	0.976	1.950	0.970	0.947	0.953	99.39
3	0.998	1.952	2.920	1.940	3.787	3.810	
3	0.998	2.928	3.890	2.910	8.520	8.573	
3	0.998	3.904	4.860	3.880	15.148	15.241	
∑N=12		∑X=9.760		∑Y= 9.700	∑XY= 28.402	$\sum X^2$= 28.577	

TABLE V. Recovery studies of triflupromazineby standard drug addition method.

Number of Observation (N)	Amount Present (Pure) (mg)	Amount of Drug Added (mg) X	Total Amount of Drug Obtained by Calculation (mg)	Amount of Drug Obtained by Calculation (mg) Y	XY	X^2	Recovery (%)
3	0.998	0.982	1.958	0.973	0.955	0.964	98.90
3	0.998	1.964	2.931	1.946	3.822	3.857	
3	0.998	2.946	3.904	2.919	8.560	8.679	
3	0.998	3.928	4.877	3.892	15.288	15.429	
∑N=12		∑X=9.820		∑Y= 9.730	∑XY= 28.625	$\sum X^2$= 28.929	

TABLE VI. Recovery studies of trifluoparazineby standard drug addition method.

Number of Observation (n)	Amount Present (pure) (mg)	Amount of Drug Added (mg) X	Total Amt Of Drug Obt. By Calculation (mg)	Amount of Drug Obtained By Calculation (mg) Y	XY	X^2	Recovery (%)
3	0.994	0.986	1.957	0.974	0.960	0.972	98.78
3	0.994	1.972	2.931	1.948	3.841	3.889	
3	0.994	2.958	3.905	2.922	8.643	8.750	
3	0.994	3.944	4.879	3.896	15.366	15.555	
∑N=12		∑X=9.860		∑Y= 9.740	∑XY= 28.810	$\sum X^2$= 29.166	

III. Result and Discussion

It has been mentioned in (Table I), the stoichiometric ratio between Cu (III) reagent and Antihistamine drugs such as Chlorpromazine (1:4), Prochloroperazine Maleate (1:4), Promethazine (1:4), Triflupromazine (1:2) and Trifluoparazine (1:4) in pure form and in their pharmaceutical preparations. This ratio remains constant even under varying reaction conditions i.e., change in reaction time, concentration of reagent and reaction temperature etc. A particular reaction time was needed for completion of the reaction and for concordant and accurate results. It varies from one compound to another. At a reaction time lesser than the described (Table II), inaccurate results are obtained because of incomplete reaction. The increase in reaction time does not change percentage recovery of the sample because the reaction is completed at a certain time.

The use of sulfuric acid as a proper reaction medium has also been studied. Sulfuric acid gives quantitative and stoichiometric results with Chlorpromazine and Prochloroperazine Maleate. The same results were obtained in the case of other samples. Reaction was also carried out in the absence of sulfuric acid. In this case, it was found that the reaction is slow and the percentage error is very high. So it was observed that a proper reaction medium is very necessary for the accurate results. After variation in the concentration of volume of sulfuric acid, it was observed that the use of 5 mL of 5 N sulfuric acid was necessary for suitable reaction medium.

Cu (III) is the main active agent, which reacts with Antihistamine drugs and 5 mL of 0.035 N Cu (III) was sufficient for all the samples for accurate results. Reaction was also carried out at lower and higher concentration at variable volumes of Cu (III). In this case, it was observed that the concentration and volume other than the prescribed under reaction conditions gives lesser recovery because of insufficient reagent. Higher concentration and volume does not give any improvement over the results. Therefore prescribed concentration and volume of the Cu (III) reagent was used. The effect of temperature has also been studied. It was observed that results improve with increase in reaction time. The best recovery was obtained at room temperature (25-

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30^0C). An increase in the reaction temperature above 25-30^0C gives inaccurate results. It happens due to the decomposition of reagent at higher temperature. At a lower temperature upto 5^0C it was observed that the reaction is very slow and needs more reaction time. It gives higher percentage error.

IV. INTERFERENCES

It is observed the presence of easilyoxidizable substance like thiourea, ascorbic acid, hydrazine; alcohols etc. interfere in the estimation. In such case higher recovery is obtained because the compounds react with the reagent. Therefore the presence of such substances should be avoided. Excipients like starch, calcium carbonate, sodium carbonate, cellulose, magnesium tri-silicate, tri-calcium phosphate and gum acacia if present in the pharmaceutical preparations do not interfere in the estimation.

V. CONCLUSION

Survey of literature shows that Cu (III) has widely been used for the analysis of several groups of compound but there is no reference regarding estimation of the compounds referred in the papers. Our experiments show that the estimation of Antihistaminedrugs by this reagent is quite satisfactory and accurate. For every compound reaction conditions were developed. Reaction time variations, concentration of reagent, reaction temperature were studied and standard method was developed. Stoichiometry of reaction was also established for every compound. To prove the authenticity of the method, % recovery and recovery experiments were done. For each sample size at least nine determinations were done and result calculated. The method is simple convenient and does not need any sophisticated equipment for analysis.

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