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New oxidative determination of some new Antihypertensive drugs in pure form and in their pharmaceutical preparations with Cu (III) reagent

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Abstract: *In the present paper we have reported a simple and convenient titrimetric method for the determination of some Antihypertensive drugs in pure form and in their pharmaceutical preparations e.g. Propranolol, Metroprolol, Methyldopa, Labitalol and Enolopril by using Potassiumdipertelluratocuprate (III) as an oxidizing reagent. The present reagent is being used for the oxidation of several class of organic compounds. Aliquots containing 1-5mg of the sample were taken in 100mL stoppered conical flask, 5ml of 0.035N Potassiumdipertelluratocuprate (III) and 10mL of 5N 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 5mL of 10% KI solution was added to it. Contents shaken thoroughly and allowed to stand for a minute. The liberated iodine was titrated with 0.01N 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. In Indian pharmacopoeia (IP) 2007, vol. 2, the determination of Labetalol and Methyldopa tablets are given by Infrared Absorption Spectroscopy (page 1274 & 1368), Propranolol Hydrochloride is also determined by Infrared Absorption Spectroscopy IP 2007 Vol. 3 (page 1609). While for rest Antihypertensive drugs used there is no method available in IP.*

Key words: *Antihypertensive drugs, Potassiumdipertelluratocuprate (III) Reagent, titration.*

I. Introduction

A numbers of compounds have been used for controlling hypertensive activities in different types of diseases. Antihypertensive drugs are used to prevent hypertension (high blood pressure) complications of like stroke and myocardial infarction. Propranolol [1,2]-(RS)-1- (1-methylethylamino)-3- (1-naphthyloxy) propan-2-ol) is a sympatholytic non-selective beta blocker. Propranolol is also used to lower portal vein pressure in portal hypertension and prevent esophageal variceal bleeding. Enalapril [3,4] (2S)-1-[(2S)-2- {[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2-yl] amino}propanoyl] pyrrolidine-2-carboxylic acid is an angiotensin-converting-enzyme (ACE) inhibitor [4] used in the treatment of hypertension, diabetic nephropathy, and some types of chronic heart failure. Enalapril was the first member of the group known as the dicarboxylate-containing ACE inhibitors. Enalapril has been proven to protect the function of the kidneys in hypertension, heart failure, and diabetes. Methyldopa [5-7] (L-α -Methyl-3,4-**d**ihydr**o**xy**p**henyl**a**lanine)(S)-2-amino-3-(3,4-dihydroxyphenyl)-2-methyl propanoic acid) is an alpha-adrenergic agonist psychoactive drug used as a sympatholytic or antihypertensive. Labetalol [8-9] (RS)-2-hydroxy-5-{1-hydroxy-2-[(1-methyl-3-phenylpropyl) amino] ethyl} benzamide) is a mixed alpha/ beta adrenergic antagonist, which is used to treat high blood pressure. It has a particular indication in the treatment of pregnancy-induced hypertension which is commonly associated with pre-eclampsia. Metoprolol [10] (RS)-1-(Isopropylamino)-3-[4-(2-methoxyethyl)phenoxy] propan-2-ol is a selective β_1 receptor blocker used in treatment of several diseases of the cardiovascular system, especially hypertension [11]. The active substance metoprolol is employed either as metoprolol succinate or as metoprolol tartrate Metoprolol is used for a number of conditions including: hypertension, angina, acute myocardial infarction, supraventricular tachycardia, ventricular tachycardia, congestive heart failure, and prevention of migraine headaches.

Because of the great medicinal value, their estimation has widely been studied [1-10]. Most of the methods used for the determination of Antihypertensive drugs involve sophisticated instruments and complicated techniques. In the present paper a new simple titrimetric method has been described for the determination of Antihypertensive drugs with Cu(III) reagent. In Indian pharmacopoeia (IP) 2007, vol. 2, the determination of Labetalol and Methyldopa tablets are given by Infrared Absorption Spectroscopy (page 1274 & 1368), Propranolol Hydrochloride is also determined by Infrared Absorption Spectroscopy IP 2007 Vol. 3 (page 1609). While for rest Antihypertensive drugs used there is no method available in IP.

II. Experimental

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. 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.

Standardisation of Cu (III) Reagent

Aliquots (5mL) 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. A blank was also run.
Stock solution (Aqueous) of sodiumthiosulphate (0.01N) (Merk) was prepared and standardized by (Merk) 0.01N potassium dichromate solution iodometrically. Aqueous solution of Potassium iodide (Baker analyzed reagent) and (10% w/v) starch were also prepared.

Sample Solution

Accurately weighed (100 mg) pure sample of Azithromycin, Azenam, Kenamycin, Gemifloxacin and Clindamycin 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 .

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.

III. 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 minuts) 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 (0.01N) 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.

IV. Calculation

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

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.

Table No1: Miligram determination of Antihypertensive drugs with Cu(III) reagent

S. No.	Sample	Aliquots taken (mL)	Amount present* (mg)	Reaction time (min.)	Molecularity (n)	Amount obtained by calculation**	Error (%)	SD	CV
1.	Propranolol pure	1	0.9992	15	8	0.9830	-1.62	0.0081	0.0171
		3	2.9978	15	8	2.9746	-0.77	0.0011	0.0229
		5	4.9960	15	8	4.9786	-0.35	0.0013	0.0293
A	Ciplar tab	1	0.9912	15	8	0.9780	-1.32	0.0022	0.0049
		3	2.9736	15	8	2.9578	-0.53	0.0029	0.0058
		5	4.9560	15	8	4.9328	-0.46	0.0022	0.0448
B	Inderal Tab	1	1.0020	15	8	0.9886	-1.34	0.0013	0.0268
		3	3.0060	15	8	2.9866	-1.32	0.0016	0.0315
		5	5.0100	15	8	4.9664	-0.87	0.0010	0.0205
2	Labetalol	1	0.9978	15	8	0.9842	-1.36	0.041	0.0082
		3	2.9934	15	8	2.9640	-0.98	0.018	0.0364
		5	4.9990	15	8	4.9700	-0.58	0.0011	0.0221
A	Lobet Tab	1	0.9890	15	8	0.9698	-1.92	0.0092	0.0184
		3	2.9670	15	8	2.9460	-0.70	0.0081	0.0171
		5	4.9450	15	8	4.9256	-0.39	0.0012	0.0243
B	Normadate Tab	1	0.9884	15	8	0.9780	-1.04	0.0012	0.0243
		3	2.9652	15	8	2.9342	-1.03	0.0066	0.1336
		5	4.9420	15	8	4.9008	-0.82	0.0091	0.1845
3	Metoprolol pure	1	0.9994	10	5	0.9884	-1.10	0.0012	0.0243
		3	2.9982	10	5	2.9800	-0.61	0.0053	0.1068
		5	4.9910	10	5	4.9898	-0.02	0.0088	0.1767
A	Betaloc Tab	1	1.0020	10	5	0.9798	-2.22	0.0012	0.0243
		3	3.0060	10	5	2.9836	-0.75	0.0051	0.1811
		5	5.0100	10	5	4.9996	-0.21	0.0048	0.1015
B	Metolar Tab	1	1.0010	10	5	0.9862	-1.48	0.0021	0.2278
		3	3.0030	10	5	2.9636	-1.31	0.0022	0.0792
		5	5.0050	10	5	4.9806	-0.49	0.0033	0.0711
4	Enalopril Pure	1	0.9920	15	5	0.9840	-0.80	0.0078	0.7911
		3	2.9760	15	6	2.9528	-0.77	0.0061	0.2061
		5	4.9600	15	6	4.9240	-0.72	0.0064	0.1297
A	Dilvas Tab	1	0.9860	15	6	0.9712	-1.48	0.0076	0.7932
		3	2.9580	15	6	2.9280	-1.00	0.0058	0.1978
		5	4.9390	15	6	4.9002	-0.78	0.0062	0.1279
B	Enamate Tab	1	0.9884	15	6	0.9710	-1.74	0.0015	0.1611
		3	2.9652	15	6	2.9338	-1.04	0.0014	0.0499
		5	4.9420	15	6	4.9000	-0.84	0.0025	0.0534
5	Methyldopa	1	0.9900	10	4	0.9830	-0.70	0.0040	0.4069
		3	2.9700	10	4	2.9504	-0.65	0.0053	0.1798
		5	4.9500	10	4	4.9266	-0.47	0.0044	0.0892
A	Aldomet Tab	1	0.9798	10	4	0.9588	-2.10	0.0033	0.3381
		3	2.9394	10	4	2.9182	-0.71	0.0078	0.2651
		5	4.8990	10	4	4.8542	-0.86	0.0077	0.1621
B	Dopagyt tab	1	0.9988	10	4	0.9890	-0.98	0.0034	0.3444
		3	2.9978	10	4	2.9688	-0.97	0.0032	0.1169
		5	4.9990	10	4	4.9550	-0.88	0.0025	0.0547

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

For testing authenticity of the recommended procedure standard deviation (SD) and coefficient of variation (CV) were also calculated. At least nine determinations were carried out and the results noted. The proposed method was further justified by recovery experiments through standard drug addition method. A known amount of the pure compound was taken and to this, varying amounts of pharmaceutical product of the same compounds were added. The total amount of the sample was found by the usual method.

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

Where, N= Total no. of observations, X= Amount of drug added, Y= Amount of drug obtain by calculation.

Table 2: Recovery experiments of Antibiotic drugs by standard drug addition method.

Name of the drugs	S. No.	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 (%)
Propranolol Hydrochloride	1	3	0.9992	0.9830	1.9422	0.9780	0.9614	0.9984	99.20
	2	3	0.9992	1.9660	2.9252	1.9560	3.8455	3.8651	
	3	3	0.9992	2.9490	3.8982	2.9340	8.6524	8.6966	
	4	3	0.9992	3.9320	4.8712	3.9120	15.3820	15.4606	
		∑N=12		∑=9.8348		∑=9.7800	∑=28.8413	∑=29.0200	
Labetalol	1	3	0.9978	0.9842	1.9120	0.9698	0.9545	0.9686	98.12
	2	3	0.9978	1.9684	2.8762	1.9396	3.8179	3.8746	
	3	3	0.9978	2.9526	3.8504	2.9094	8.5903	8.7178	
	4	3	0.9978	3.9368	4.8346	3.8792	15.2716	15.4984	
		∑N=12		∑=9.8420		∑=9.6698	∑=28.6343	∑=29.0594	
Metoprolol	1	3	0.9994	0.9884	1.9240	0.9798	0.9684	0.9769	99.07
	2	3	0.9994	1.9768	2.9098	1.9596	3.8737	3.9077	
	3	3	0.9994	2.9652	3.8422	2.9394	8.7159	8.7924	
	4	3	0.9994	3.9536	4.8450	3.9192	15.4950	15.6309	
		∑N=12		∑=9.8840		∑=9.7940	∑=29.0530	∑=29.3079	
Enalopril	1	3	0.9920	0.9840	1.8842	0.9712	0.9557	0.9682	98.71
	2	3	0.9920	1.9680	2.9090	1.9424	3.8246	3.8730	
	3	3	0.9920	2.9520	3.8850	2.9136	8.6006	8.7243	
	4	3	0.9920	3.9360	4.8720	3.8848	15.2905	15.4921	
		∑N=12		∑=9.8400		∑=9.7120	∑=28.6716	∑=29.0576	
Methyldopa	1	3	0.9900	0.9830	1.9500	0.9588	0.9425	0.9663	98.99
	2	3	0.9900	1.9660	2.9224	1.9176	3.7700	3.8651	
	3	3	0.9900	2.9490	3.9006	2.8764	8.4825	8.6966	
	4	3	0.9900	3.9320	4.8804	3.8352	15.0800	15.4606	
		∑N=12		∑=9.8300		∑=9.5878	∑=28.2750	∑=28.9886	

V. Result And Discussion

The reaction conditions were established after studying effect of variables such as reaction time, concentration of the reagent, amount of reagent, sulphuric acid and reaction temperature. In the determination of Propranolol, Labitalol, Metroprolol, and Enolopril Methyldopa in pure form and in their pharmaceutical preparation constant results were obtained at 15, 15, 10, 15 and 10 minutes respectively. A much more reaction time than the prescribed one does not improve results. The percentage recovery of sample was fairly low at a lesser reaction time due to incomplete reaction. It was also established that the prescribed concentration of the reagent (0.035N) was suitable for accurate results. The effect of concentration of Cu (III) reagent and sulphuric acid was studded and it was found that the recommended concentration of both reagents were suitable for the completion of reaction. While studying the effect of temperature it was observed that the reaction was completed at room temperature (25-30^{0}C). On heating the reaction mixture directly on flame or on boiling water bath inaccurate results were obtained. It may be due to decomposition of the reagent. Results given in table no.1 show % error, standard deviation (SD), and coefficient of variation (CV). This indicates that the suggested method is reproducible and precise. It can easily be adopted in any pharmaceutical laboratory.

VI. 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 antibiotics 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.

Interference

Excipients like starch, calcium carbonate, sodium carbonate, cellulose, magnesium trisilicate, tricalcium phosphate and gum acacia if present in the pharmaceutical preparations do not interfere in the estimation.

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