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A New method For Quantitative estimation And Assay Of Some Anti arrhythmic Agents By Using Cu (III)Reagent

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Abstract: *In present work we have developed a new and simple method for analysis of some Antiarrhythmic drugs inpure form and in their pharmaceutical preparations. This method isbased on simple oxidation-reduction titration with a new synthesized Potassiumdipertelluratocuprate (III) reagent. Some Antiarrhythmic drugs are selected and oxidized with new Cu (III) reagent and then iodometric titration is performed with standard sodiumthiosulphatesolution using starch as an indicator.Cu (III) reagent is an excellent and oxidized several function groups oforganic compoundsand the results are compared with Indian Pharmacopeia (IP) and assay noted. The value of percentage error, standard deviation (SD) and coefficient of variation (CV) 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.*

Key words: *Cu(III) reagent, antiarrhythmic drugs, standard deviation, percentage recovery.*

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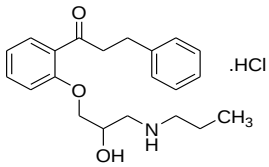
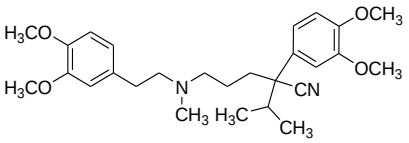
I. Introduction

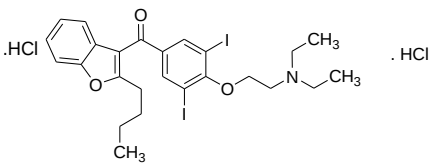
Antiarrhythmic Agents used for the treatment or prevention of cardiac arrhythmias[1]. They may affect the polarization-repolarization phase of the action potential, its excitability or refractoriness, or impulse conduction or membrane responsiveness within cardiac fibers. Antiarrhythmic drugs are the special type of medicines that correct irregular heartbeats and slow down hearts that beat too fast. Antiarrhythmic drugs are used to treat abnormal heart rhythms resulting from irregular electrical activity of the heart[2].



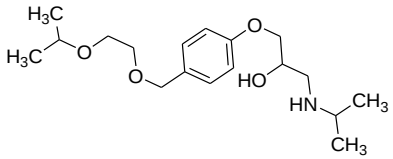
Propafenone Hydrochloride



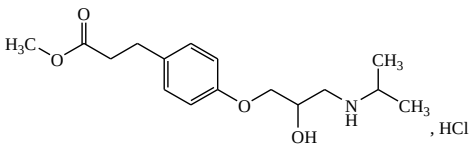
Verapamil hydrochloride



Amiodarone Hydrochloride



Bisoprolol



Esmolol Hydrochloride

Propafenone Hydrochloride($C_{21}H_{27}NO_3$.HCl) IUPAC Name: 1-{2-[2-Hydroxy-3-(propylamino) propoxy] phenyl}-3-phenylpropan-1-one. Propafenone Hydrochloride is treating certain types of life-threatening irregular heartbeat (ventricular arrhythmias)[3]. It is also used to help maintain a normal heart rhythm in certain patients who have certain types of irregular heartbeat[4]. Verapamil hydrochloride($C_{27}H_{38}N_2O_4$)HCl Molecular mass IUPAC:(*RS*)-2-(3,4-Dimethoxyphenyl)-5-{[2-(3,4-dimethoxyphenyl)ethyl]-(methyl) amino}-2-prop-2-ylpentane- nitrile. Verapamil hydrochloride sold under various trade names is a medication used for the treatment of high blood pressure, chest pain from not enough blood flow to the heart, and supraventricular tachycardia. It may also be used for the prevention of migraines and cluster headaches[5].

Amiodarone hydrochloride($C_{25}H_{29}I_2NO_3$.HCl) IUPAC: (2-{4-[(2-butyl-1-benzofuran-3-yl) carbonyl]-2, 6-diiodo -phenoxy} ethyl) diethylamine chloride. Amiodarone hydrochloride is an antiarrhythmic agent used for various types of cardiac dysrhythmias,both ventricular and atrial. It was discovered in 1961. It is used in the treatment of a wide range of cardiac tachyarrhythmias, including both ventricular and supraventricular arrhythmias[6].

Bisorolol($C_{18}H_{31}NO_4$)IUPAC: [2-hydroxy-3-(4-{[2-(propan-2-yloxy) ethoxy] methyl} phenoxy)

propyl] (propan-2-yl) amine. Bisoprolol is white powder and soluble in water and methanol. Bisoprolol is a cardio selective β1-adrenergic blocking agent used for secondary prevention of myocardial infarction (MI), heart failure, angina pectoris and mild to moderate hypertension[7].

Esmolol Hydrochloride: $C_{16}H_{25}NO_4.HCl$, IUPAC: 2-hydroxy-3-[4-(3-methoxy-3-oxopropyl) phenoxy]-*N*-(propan-2-yl) propan-1-aminium chloride. Esmolol hydrochloride is white powder and soluble in water. Esmololhydrochloride is a cardioselective β_1 receptor blocker with rapid onset, a very short duration of action, and no significant intrinsic sympathomimetic or membrane stabilizing activity at therapeutic dosages[8].

These drugs have a large importance for the health of human being so their analysis is important. These drugs are oxidized analyzed with Cu (III) reagent. The reagent can be prepared by using following method.

II. Experimental

Synthesis of Cu (III) Reagents

Potassiumdipertelluratocuprate (III) reagent[9-11] $K_5H_4[Cu(TeO_6)_2].\ 18H_2O$(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.

Standardization of Cu (III) Reagent[12-14]

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.

Solution Preparation

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 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.

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.

General Procedure[15]

An aqueous acidic solution containing 5mg of the sample was taken in a 100mL stoppered conical flask and 5mL of 0.035N Cu(III) reagent and 5mL of 5N sulfuric acid was added to it. The reaction mixture was shaken thoroughly and allowed to react for 15minutes at room temperature (25-30^{0}C). After the reaction is over 5mL of 5% potassium iodide was added to it. Contents were shaken thoroughly and allowed to react for a minute. The unconsumed Cu(III) was determined iodometrically. A blank experiment was also run under identical conditions using all the reagents except sample. The amount of Cu(III) consumed for the sample was calculated with the difference in the titer value of sodium thiosulphate solution for blank and actual experiments. The recovery of the sample was calculated with the amount of Cu(III) consumed for the sample.For every sample percentage error, standard deviation coefficient of variation and percentage recovery were calculated.

Calculation

Amount present

mg of sample = $\dfrac{M \times N(B-S)}{n}$ 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.

Percentage error

Percentage error=

$$\frac{(Xa - Xb)}{Xb} \times 100$$

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

Standard Deviation

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

Where, $\overline{X}$ = 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 Variations $CV = \frac{SD \times 100}{\overline{X}}$

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

Recovery experiment

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, ΣY = ΣNY,
ΣXY = Σ (NX) (Y), ΣX^2 = Σ (NX) (X)

Sample	Aliquots taken (mL)	Amount present* (mg)	Reaction time (min.)	Molecularity (n)	Amount obtained **	Error(%)-	SD	CV
Propafenone. HCl (Pure)	1	0.996	10	4	0.979	1.71	0.0062	0.6333
	3	2.988	10	4	2.970	0.60	0.0062	0.2020
	5	4.980	10	4	4.962	0.36	0.0142	0.2862
Rytmonorm (Tab.)	1	0.976	10	4	0.961	1.54	0.0069	0.7180
	3	2.928	10	4	2.915	0.44	0.0062	0.2127
	5	4.880	10	4	4.863	0.35	0.0070	0.1439
Propafenone 300 (Tab.)	1	0.981	10	4	0.965	1.63	0.0057	0.5810
	3	2.943	10	4	2.929	0.48	0.0062	0.2117
	5	4.905	10	4	4.889	0.33	0.0119	0.2434
Verapamil.HCl (Pure)	1	0.988	10	6	0.973	1.52	0.0040	0.4111
	3	2.964	10	6	2.956	0.27	0.0045	0.1522
	5	4.940	10	6	4.930	0.20	0.0045	0.0913
Isoptin (Tab.)	1	0.986	10	6	0.976	1.01	0.0047	0.4816
	3	2.958	10	6	2.947	0.37	0.0048	0.1629
	5	4.930	10	6	4.921	0.18	0.0020	0.0406
Calaptin (Tab.)	1	0.964	10	6	0.952	1.24	0.0045	0.4727
	3	2.892	10	6	2.882	0.34	0.0040	0.1387
	5	4.820	10	6	4.813	0.15	0.0045	0.0934
Amiodarone.HCl (Pure)	1	0.992	10	6	0.976	1.61	0.0060	0.6148
	3	2.976	10	6	2.962	0.47	0.0053	0.1789
	5	4.960	10	6	4.947	0.26	0.0060	0.1213
Cardarone (Tab.)	1	0.964	10	6	0.951	1.35	0.0027	0.2839
	3	2.892	10	6	2.883	0.31	0.0053	0.1838
	5	4.820	10	6	4.813	0.15	0.0060	0.1309
Cardasone (Amp.)	1	0.972	10	6	0.960	1.23	0.0060	0.6250
	3	2.916	10	6	2.895	0.72	0.0053	0.1831
	5	4.860	10	6	4.846	0.29	0.0063	0.1300
Bisoprolol (Pure)	1	0.985	10	4	0.972	1.32	0.0053	0.5453
	3	2.955	10	4	2.935	0.68	0.0063	0.2147
	5	4.925	10	4	4.911	0.28	0.0055	0.1120
Biselect	1	0.958	10	4	0.941	1.77	0.0060	0.6376

(Tab.)	3	2.874	10	4	2.855	0.66	0.0055	0.1926
	5	4.790	10	4	4.783	0.15	0.0052	0.1086
Cadrol (Tab.)	1	0.978	10	4	0.961	1.74	0.0060	0.6243
	3	2.934	10	4	2.925	0.31	0.0058	0.1983
	5	4.890	10	4	4.882	0.16	0.0060	0.1229
Esmolol.HCl(Pure)	1	0.989	10	4	0.976	1.31	0.0069	0.7070
	3	2.967	10	4	2.955	0.40	0.0047	0.1591
	5	4.945	10	4	4.929	0.32	0.0047	0.0954
Cardesmo (Tab.)	1	0.978	10	4	0.965	1.33	0.0065	0.6736
	3	2.934	10	4	2.925	0.31	0.0031	0.1060
	5	4.890	10	4	4.881	0.18	0.0035	0.0717
Neotach (Tab.)	1	0.966	10	4	0.954	1.24	0.0070	0.7338
	3	2.898	10	4	2.877	0.72	0.0062	0.2142
	5	4.830	10	4	4.823	0.14	0.0065	0.1348

Table 1: Milligram determination of some Antiarrhythmicdrugs in pure form and in their pharmaceutical preparations with (0.035) Cu (III)reagent in acidic medium

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

Table 2: Recovery studies of Propafenone hydrochloride by standard drug additionmethod.

Observation (N)	Amount present (Pure)(mg)	Drug added (mg) X	Total amount obtained (mg)	Amount drug obtained Y	XY	X^2	Recovery (%)
3	0.996	0.976	1.940	0.961	0.938	0.953	
3	0.996	1.952	2.901	1.922	3.752	3.810	
3	0.996	2.928	3.862	2.883	8.441	8.573	98.46
3	0.996	3.904	4.823	3.844	15.007	15.241	
∑N=12		∑X=9.760		∑Y=9.610	∑XY=28.138	∑X2=28.577	

Table 3: Recovery studies of Verapamil hydrochloride by standard drug addition method.

Observation (N)	Amount present (Pure)(mg)	Drug added (mg) X	Total amount obtained (mg)	Amount drug obtained (mg) Y	XY	X^2	Recovery (%)
3	0.988	0.986	1.949	0.976	0.962	0.972	
3	0.988	1.972	2.925	1.952	3.849	3.889	
3	0.988	2.958	3.901	2.928	8.661	8.750	98.98
3	0.988	3.944	4.877	3.904	15.397	15.555	
∑N=12		∑X=9.860		∑Y= 9.760	∑XY= 28.869	$\sum X^2$=29.166	

Table 4: Recovery studies of Amiodarone hydrochloride by standard drug addition method.

Observation (N)	Amount present (Pure)(mg)	Drug added (mg) X	Total amount obtained (mg)	Amount drug obtained (mg) Y	XY	X^2	Recovery (%)
3	0.992	0.964	1.927	0.951	0.917	0.929	
3	0.992	1.928	2.878	1.902	3.667	3.717	
3	0.992	2.892	3.829	2.853	8.251	8.364	98.65
3	0.992	3.856	4.780	3.804	14.668	14.869	
∑N=12		∑X=9.640		∑Y= 9.510	∑XY= 27.503	∑X2=27.879	

Table 5: Recovery studies of Bisoprolol by standard drug addition method.

observation (N)	Amount present (Pure)(mg)	Drug added (mg) X	Total amount obtained (mg)	Amount drug obtained (mg) Y	XY	X^2	Recovery (%)
3	0.985	0.958	1.913	0.941	0.927	0.918	
3	0.985	1.916	2.854	1.882	3.606	3.671	
3	0.985	2.874	3.795	2.823	8.113	8.260	98.35
3	0.985	3.832	4.736	3.764	14.424	14.684	
∑N=12		∑X=9.580		∑Y= 9.410	∑XY= 27.070	∑X2=27.533	

Table 6: Recovery studies of Esmolol hydrochloride by standard drug addition method.

bservation (N)	Amount present (Pure)(mg)	Drug added (mg) X	Total amount obtained (mg)	Amount drug obtained (mg) Y	XY	X^2	Recovery (%)
3	0.989	0.978	1.941	0.965	0.944	0.956	
3	0.989	1.906	2.906	1.830	3.579	3.826	
3	0.989	2.934	3.871	2.895	8.494	8.608	98.12
3	0.989	3.918	4.836	3.860	15.100	15.304	
∑N=12		∑X=9.780		∑Y= 9.550	∑XY= 28.117	$\sum X^2$=28.694	

III. Result And Discussion

The stoichiometric ratio between Cu(III) reagent and antiarrhythmic drugs such as Propafenone hydrochloride (1:4), Verpamil hydrochloride (1:6), amiodarone hydrochloride (1:6), bisoprolol (1:4) and esmolol (1:4) in pure form and in their pharmaceutical preparations. It has been mentioned in (Table-1). At a reaction time lesser than the described inaccurate results are obtained because of incomplete reaction. The increase in reaction time than the prescribed one 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 amiodarone hydrochloride and bisoprolol. 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 5mL of 5N sulfuric acid was necessary for suitable reaction medium.

IV. Conclusion

Survey of literature shows that Cu (III) has widely been used for the analysis of several compounds but there is no reference regarding estimation of the compounds referred in the papers. Our experiments show that the estimation of antiarrhythmic 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 at least nine determinations were done and resultsare calculated.

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