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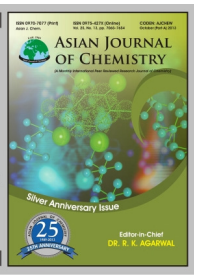

Assay of Some Antimalarial Drugs in Pure Form and in Their Pharmaceutical Preparations with Pyridinium Fluorochromate Reagent

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In the present paper, we have reported a simple and convenient titrimetric method for determination of antimalarial drugs *e.g.*, chloroquine phosphate, amodiaquine hydrochloride, mefloquine hydrochloride, primaquine phosphate and quinine sulphate in pure form and in their pharmaceutical preparations such as lariago, resochin, camoquin, flavoquine, mefloquin, meflotas, maliride, malquine, quinersol and rezquine tablets with pyridinium fluorochromate reagent. It is a versatile oxidizing agent of chromium(VI) and is being widely used as an oxidant for several classes of organic compounds. During estimation it was noted that the excipients present in pharmaceutical preparations do not interfere. The value of percentage error, coefficient of variation and standard deviation 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: Antimalarial drugs, Pharmaceutical preparations, Pyridinium fluorochromate, Oxidizing agent, Titration.

INTRODUCTION

A variety of compounds containing chromium(VI) have proved to be versatile reagents capable of oxidizing almost every oxidizable functional group[1]. Extensive work has led to the development of a good number of such oxidants like Collins reagent[2], chromium trioxide-3,5-dimethylpyrazole complex[3], pyridinium chlorochromate[4], pyridinium dichromate[5], 2,2'-bipyridinium chlorochromate[6], pyridinium fluorochromate[7,8], quinolinium fluorochromate[9], quinolinium chlorochromate[10], 3,5-dimethylpyrazolium fluorochromate[11], 2,6-dicarboxypyridinium chlorochromate[12,13], N-methylpiperidinium chlorochromate[14], tetramethylammonium fluorochromate[15] and benzyltrimethylammonium fluorochromate[16].

Industrial demands have led many workers to search for more ideal oxidants with a number of specifications including lower cost, higher yields, better selectivity, milder neutral conditions, easier preparations, high solubility, less toxicity and short reaction times. Among the above mentioned reagents[2-16], pyridinium fluorochromate (PFC) has an edge over others for rendering higher yields in neutral conditions. In the present manuscript we have taken pyridinium fluorochromate as an oxidizing reagent which has been synthesized in the laboratory[17].

Malaria is caused by protozoan parasites of the genus Plasmodium. In human beings 80 % malaria is caused mostly by *P. falciparum*, *P. malariae*, *P. ovale*, *P. vivax* and *P. knowlesi*. Chloroquine is a 4-aminoquinoline drug and has a high value of distribution. Amodiaquine has been shown to be more effective than chloroquine in treating CRPF (chloroquine resistant plasmodium falciperum) malarial infections and may afford more protection than chloroquine when used as weekly prophylaxis. Amodiaquine, like chloroquine, is generally well tolerated. Mefloquine is a chiral molecule with two asymmetric carbon centers and is currently manufactured and sold as a racemate of the (+/-) R, S enantiomers by different pharmaceutical companies. Recent research shows that the (+) enantiomer is more effective in treating malaria and the (-) enantiomer specifically binds to adenosine receptors in the central nervous system, which may explain some of its psychotropic effects. Primaquine is mainly used to treat the *P. vivax* and *P. ovale* malaria.

EXPERIMENTAL

Pyridinium fluorochromate (PFC) solution (0.03 N): 495 mg of pyridinium fluorochromate was dissolved in 150 mL of glacial acetic acid (Merck) and made up to the volume with distilled water in 250 mL volumetric flask. The solution was standardised iodometrically.

Sodium thiosulphate solution (0.01 N): Stock solution of sodium thiosulphate was prepared by dissolving 2.4819 g of the compound in distilled water in 1000 mL volumetric flask and made up to the mark with distilled water. The solution was standardized by 0.01 N potassium dichromate solution iodometrically.

Potassium dichromate solution (0.01 N): The solution was prepared by dissolving 0.2452 g of $K_2Cr_2O_7$ in distilled water in 500 mL volumetric flask.

Potassium iodide (Baker analyzed reagent): 10 % w/v aqueous solution was prepared in distilled water.

Starch solution: 1 % w/v aqueous solution of starch was prepared in distilled water.

Sample solution: Accurately weighed (100 mg) pure samples as well as pharmaceutical preparation of chloroquine phosphate and primaquine phosphate were dissolved in minimum amount of distilled water. Amodiaquine hydrochloride, mefloquine hydrochloride and quinine sulphate were dissolved in minimum amount of ethanol. After getting a clear solution the flask was made up to the mark with distilled water. While diluting with distilled water every care was taken to keep the solution homogeneous.

Tablet solutions: Twenty tablets of pharmaceutical products were crushed to a fine powder. The powder equivalent to 100 mg of sample was taken in 100 mL calibrated volumetric flask and dissolved in the same way as described for the pure sample.

Injection solutions: As described above the contents of the injection equivalent to 100 mg of the pure sample were taken and dissolved in distilled water in 100 mL volumetric flask to get a concentration of 1 mg/mL.

General procedure: Aliquots containing 1-5 mg of the samples were taken in 100 mL stoppered conical flask and 5 mL of 0.03 N pyridinium fluorochromate 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 at room temperature (25-30 ºC) for amodiaquine hydrochloride, mefloquine hydrochloride, primaquine phosphate and quinine sulphate need 10 min whereas chloroquine phosphate require 15 min. After the reaction was over 5 mL of 10 % KI solution was added to it, contents shaken thoroughly and allowed to stand for 1 min. The liberated iodine was titrated with 0.01 N sodium thiosulphate using starch as indicator. A blank experiment was also run under identical conditions using all the reagents except the sample. The amount of the sample recovered was calculated by the difference in the titre values of sodium thiosulphate solution for blank and actual experiment.

Calculation: For each experiment, the amount of the compound was calculated by following expression:

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

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 testing quantitative validity of the recommended method, standard deviation (SD) and coefficient of variation (CV) were also calculated for each sample size. At least nine determinations were carried out and the results were noted. To justify the validity of the proposed method, recovery experiments were carried out by the standard drug addition method. 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 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 = ΣN = total number of observations, X = amount of drug added, Y = amount of drug obtained by calculation, ΣX = ΣNX, ΣY = ΣNY, ΣXY = Σ(NX) (Y), ΣX^2 = Σ(NX) (X).

The determinations were done with varying sample size (*i.e.*, 1-10 mg) but for convenience, results have been shown only with 1, 3 and 5 mg sample size (Table-1).

For every sample of antimalarial drugs *e.g.*, chloroquine phosphate, amodiaquine hydrochloride, mefloquine hydrochloride, primaquine phosphate and quinine sulphate, recovery experiment were also done by standard drug addition method and the results were reported (Tables 2-6).

RESULTS AND DISCUSSION

It was found that the stoichiometric ratio between pyridinium fluorochromate reagent and antimalarials varies. Different stoichiometric ratio is obtained in different antimalarials such as chloroquine phosphate (1:2), amodiaquine hydrochloride (1:4), mefloqine hydrochloride (1:4), primaquine phosphate (1:2) and quinine sulphate (1:2) in pure form and in their pharmaceutical preparations. The ratio remains constant even under varying reaction conditions *i.e.*, change in reaction time, concentration of the reagent, reaction medium, rection temperature *etc*. It was observed that all the antimalarial drugs studied need 10 min to complete the reaction except chloroquinine phosphate which needs 15 min. By the allowing more reaction time (more than 10-15 min) all the compounds do not give any improvement in the results. A lesser reaction time (less than 10 min) than described limit gives higher percentage of error because of incomplete reaction. The effect of concentration of pyridinium fluorochromate reagent (0.1-1.0 N) was also studied and it was found that the recommended concentration (0.03 N) was suitable for accurate and concordant results.

The effect of concentration of sulphuric acid was also studied and it was found that in the absence of acid the reaction was slow. At low concentration of sulphuric acid (1-4 N), it gives slow reaction whereas higher concentrated acid (5-10 N), has no improvement over the result. The next variation was reaction temperature. The reactivity of the sample is very slow at ice cold temperature but increases with the rise in temperature up to room temperature (25-30 ºC). Beyond this temperature, no improvement over the result has been noticed.

On the basis of available literature and stoichiometry established, a possible course of reaction may also be suggested. Since the isolation and identification of final reaction product was not possible, it was assumed that the antimalarial drugs were oxidized to their corresponding products.

Interferences: 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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TABLE-1
MILLIGRAM DETERMINATION OF SOME ANTIMALARIAL DRUGS (PURE SAMPLE) AND ITS PHARMACEUTICAL PREPARATIONS WITH PYRIDINIUM FLUOROCHROMATE IN ACIDIC MEDIUM

S. No.	Sample	Aliquots taken (mL)	Amount present* (mg)	Reaction time (min)	Molecularity	Amount obtained by calculation** (mg)	Error (%)	SD (±)	CV
1	Chloroquine phosphate (Pure)	1.00	0.986	15	2	0.976	1.01	0.0025	0.2561
		3.00	2.958	15	2	2.937	0.71	0.0014	0.0473
		5.00	4.930	15	2	4.908	0.45	0.0037	0.0751
A	Lariago (Tab) IPCA Labs	1.00	0.956	15	2	0.946	1.05	0.0018	0.1883
		3.00	2.868	15	2	2.847	0.73	0.0053	0.1848
		5.00	4.780	15	2	4.754	0.54	0.0023	0.0481
B	Resochin (Tab) Bayer Pharma.	1.00	0.936	15	2	0.926	1.07	0.0041	0.4380
		3.00	2.808	15	2	2.788	0.71	0.0026	0.0926
		5.00	4.680	15	2	4.656	0.51	0.0015	0.0321
2	Amodiaquine hydrochloride (pure)	1.00	0.994	10	4	0.983	1.10	0.0062	0.6307
		3.00	2.982	10	4	2.961	0.70	0.0044	0.1486
		5.00	4.970	10	4	4.944	0.52	0.0032	0.0647
A	Camoquine (Tab) Pfizer	1.00	0.962	10	4	0.952	1.04	0.0022	0.2311
		3.00	2.886	10	4	2.864	0.76	0.0054	0.1885
		5.00	4.810	10	4	4.784	0.54	0.0012	0.0251
B	Flavoquine (Tab) Safoni-Aventis	1.00	0.974	10	4	0.964	1.03	0.0072	0.7469
		3.00	2.922	10	4	2.904	0.62	0.0063	0.2169
		5.00	4.870	10	4	4.849	0.43	0.0042	0.0866
3	Mefloquine hydrochloride (pure)	1.00	0.983	10	4	0.973	1.02	0.0025	0.2569
		3.00	2.949	10	4	2.928	0.71	0.0013	0.0444
		5.00	4.915	10	4	4.887	0.57	0.0037	0.0757
A	Mefloquine (Tab) Emcure Pharma	1.00	0.943	10	4	0.933	1.06	0.0015	0.1608
		3.00	2.829	10	4	2.806	0.81	0.0022	0.0784
		5.00	4.715	10	4	4.698	0.36	0.0033	0.0702
B	Meflotas (Tab) Intas	1.00	0.937	10	4	0.927	1.07	0.0036	0.3883
		3.00	2.811	10	4	2.791	0.71	0.0026	0.0932
		5.00	4.685	10	4	4.659	0.55	0.0015	0.0322
4	Primaquine phosphate (pure)	1.00	0.978	10	2	0.968	1.02	0.0062	0.6813
		3.00	2.934	10	2	2.913	0.72	0.0062	0.2264
		5.00	4.890	10	2	4.872	0.37	0.0040	0.0874
A	Maliride (Tab) IPCA	1.00	0.919	10	2	0.910	0.98	0.0062	0.6813
		3.00	2.757	10	2	2.739	0.65	0.0062	0.2264
		5.00	4.595	10	2	4.575	0.44	0.0040	0.0874
B	Malquine (Tab) Ind-Swift	1.00	0.926	10	2	0.916	1.08	0.0031	0.3384
		3.00	2.778	10	2	2.759	0.68	0.0025	0.0906
		5.00	4.630	10	2	4.611	0.41	0.0039	0.0846
5	Quinine sulphate (pure)	1.00	0.959	10	2	0.948	1.15	0.0021	0.2215
		3.00	2.877	10	2	2.852	0.87	0.0013	0.0456
		5.00	4.795	10	2	4.768	0.56	0.0015	0.0315
A	Quinersol (Tab) Cipla	1.00	0.893	10	2	0.884	1.01	0.0021	0.2376
		3.00	2.679	10	2	2.658	0.78	0.0026	0.0978
		5.00	4.465	10	2	4.446	0.43	0.0017	0.0382
B	Ledercort (Tab) Wyeth	1.00	0.896	15	2	0.887	1.00	0.0029	0.3269
		3.00	2.688	15	2	2.669	0.71	0.0019	0.0712
		5.00	4.480	15	2	4.457	0.51	0.0026	0.0583

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

TABLE-2
RECOVERY STUDIES OF CHLOROQUINE PHOSPHATE BY STANDARD DRUG ADDITION METHOD

S. No.	Number of observ. (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 (%)
1	3	0.972	0.986	1.978	0.970	0.956	0.972	99.45
2	3	0.972	1.978	2.984	1.984	3.924	3.912	
3	3	0.972	2.984	3.938	2.951	8.806	8.904	
4	3	0.972	3.978	4.964	3.958	15.745	15.824	
–	ΣN=12	–	ΣX = 9.935	–	ΣY = 9.863	ΣXY = 29.435	ΣX^2 = 29.612	

TABLE-3
RECOVERY STUDIES OF AMODIAQUINE HYDROCHLORIDE PHOSPHATE BY STANDARD DRUG ADDITION METHOD

S. No.	Number of observ. (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 (%)
1	3	0.996	0.977	1.970	0.975	0.953	0.955	
2	3	0.996	1.980	2.966	1.982	3.924	3.920	
3	3	0.996	2.981	3.982	2.961	8.827	8.886	99.14
4	3	0.996	3.979	4.985	3.962	15.765	15.832	
–	ΣN = 12	–	ΣX = 9.917	–	ΣY = 9.880	ΣXY = 29.469	ΣX^2 = 29.593	

TABLE-4
RECOVERY STUDIES OF MEFLOQUINE HYDROCHLORIDE BY STANDARD DRUG ADDITION METHOD

S. No.	Number of observ. (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 (%)
1	3	0.958	0.977	1.983	0.993	0.970	0.955	
2	3	0.958	1.983	2.976	1.939	3.845	3.932	
3	3	0.958	2.970	3.980	2.962	8.797	8.821	99.72
4	3	0.958	3.987	4.991	3.989	15.904	15.896	
–	ΣN = 12	–	ΣX = 9.917	–	ΣY = 9.883	ΣXY = 29.516	ΣX^2 = 29.604	

TABLE-5
RECOVERY STUDIES OF PRIMAQUINE PHOSPHATE BY STANDARD DRUG ADDITION METHOD

S. No.	Number of observ. (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 (%)
1	3	0.958	0.977	1.983	0.993	0.970	0.955	
2	3	0.958	1.983	2.976	1.939	3.845	3.932	
3	3	0.958	2.970	3.980	2.962	8.797	8.821	99.72
4	3	0.958	3.987	4.991	3.989	15.904	15.896	
–	ΣN=12	–	ΣX= 9.917	–	ΣY=9.883	ΣXY=29.516	ΣX^2= 29.604	

TABLE-6
RECOVERY STUDIES OF QUININE SULPHATE BY STANDARD DRUG ADDITION METHOD

S. No.	Number of observ. (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 (%)
1	3	0.939	0.984	1.969	0.928	0.913	0.968	
2	3	0.939	1.977	2.971	1.961	3.877	3.909	
3	3	0.939	2.960	3.978	2.941	8.705	8.762	99.48
4	3	0.939	3.962	4.980	3.949	15.646	15.697	
–	ΣN=12	–	ΣX = 9.883	–	ΣY=9.779	ΣXY = 29.141	ΣX^2 = 29.336	

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