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Two charge-transfer complexation reactions for spectrophotometric determination of pheniramine maleate using π-acceptors

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This study presents two simple, selective and rapid spectrophotometric methods for determination of pheniramine maleate (PAM) in pure form and in its formulations. Both methods are based on the formation of charge-transfer (CT) reaction of PAM with p-chloranilic acid (CAA) or 2,3-dichloro-5,6-dicyanoquinone (DDQ) in 1,4-dioxan-acetonitrile medium. CT complexes were quantified at 530 and 590 nm for CAA and DDQ methods, respectively. Beer's law is obeyed (conc. ranges, 12.5-200 μg ml^{-1} for CAA and 5-80 μg ml^{-1} for DDQ method), with correlation coefficients (r) of 0.9999 and 0.9991. Apparent molar absorptivities are calculated to be 1.27×10^3 and 3.06×10^3 l $mol^{-1}cm^{-1}$, respectively and corresponding Sandell sensitivities are 0.281 and 0.112 μg cm^{-2}. Developed methods were successfully applied for determination of PAM in tablets and injections.

Keywords: Charge-transfer (CT) complexation, Pharmaceuticals, Pheniramine maleate (PAM), Spectrophotometry

Introduction

Pheniramine maleate [PAM; $C_{16}H_{20}N_2{\cdot}C_4H_4O_4$; N,N-Dimethyl-3-phenyl-3-(2-pyridyl) propylamine hydrogen maleate (Fig. 1)] is a potent H_1 receptor antagonist used as antihistaminic for symptomatic relief of hypersensitivity reaction. It is used in allergic conditions, itching and mainly to prevent motion sickness, nausea, vomiting and vertigo[1]. PAM is official in United State Pharmacopeia[2] and British Pharmacopoeia[3]. Determination of PAM in biological fluids includes high-performance liquid chromatography (HPLC)[4] and gas chromatography-mass spectrometry (GC-MS)[5] methods. Several techniques (HPLC[6-13], gas-liquid chromatography (GLC)[14] capillary zone electrophoresis[15,16], capillary isotachophoresis[17], and polarography[18]) determine PAM in pharmaceuticals (bulk drug, tablets, injections, expectorants, syrups and nasal spray). PAM assay (conc. range, 8.9-89 μg ml^{-1}) is reported[19] based on the formation of 2:1 complex with Fe (III) at pH 5. Mohammed *et al*[20] presented a sensitive method (molar absorptivity 1.32×10^4 l $mol^{-1}cm^{-1}$; linear range of 5-50 μg ml^{-1}) based on interaction of PAM with quercetin (as counter ion), which after its oxidation with N-bromosuccinimide, gives a highly colored ion-pair complex in Teorell-Stenhagen buffer (pH 5.0), extracted into dichloromethane and measured at 528 nm. Charles & Fredrick[21] reported simultaneous determination of PAM and phenylephrine hydrochloride in nasal spray by solvent extraction flow injection spectrophotometry. Reported methods[19,20] are not satisfactory, showing linearity over a narrow dynamic range, critically depending on pH, using tedious and time consuming liquid-liquid extraction step and large amount of organic solvents.

This study describes application of hydroquinone derivatives [p-chloranilic acid (CAA) and 2,3-dichloro-5,6-dicyanoquinone (DDQ); excellent π-acceptors and widely used in assay of several drugs[22-25]], in the rapid, selective and sensitive spectrophotometric assay of PAM in bulk drug and in its two dosage forms. The methods depend upon interaction of PAM with CAA or DDQ to form intensely colored charge-transfer (CT) complexes in 1,4-dioxan-acetonitrile (DAN) medium.

Experimental Section

Materials

Pharmaceutical grade PAM (99.85% pure) was procured from Sanofi Aventis Pharma., Mumbai, India.

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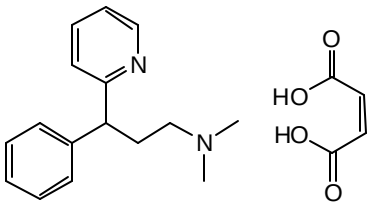


Fig. 1—Structure of pheniramine maleate

Avil tablets (25 & 50 mg) and Avil injection (all from Aventis Pharma Ltd, Thane, India) were purchased from local market. 1,4- dioxan and acetonitrile (spectroscopic grade) were purchased from Merck, Mumbai, India. Distilled water was used wherever required.

Apparatus and Reagents

All absorption were measured using a Systronics model 106 digital spectrophotometer (Systronics Ltd, Ahmedabad, India) with 1 cm path length matched quartz cells. A 0.2% CAA and DDQ (both from S.D. Fine Chem Ltd, Mumbai) were prepared freshly in 1,4-dioxan. A 250 μg ml^{-1} PAM stock solution was prepared by dissolving pure drug (25 mg) in acetonitrile in a 100 ml volumetric flask and solution was diluted to the mark with same solvent and used for CAA method. Stock solution was diluted with acetonitrile to get 100 μg ml^{-1} solution and used in DDQ method.

CAA and DDQ Methods

For CAA method, varying aliquots of standard PAM solution [equiv to 12.5-200 μg ml^{-1} (0.25 - 4.0 ml of 250 μg ml^{-1})] were accurately transferred into a series of 5 ml calibrated flasks and the total volume in each flask was brought to 4 ml by adding acetonitrile. After addition of 1 ml of 0.2 % CAA solution, content was mixed well and absorbance was measured at 530 nm against a reagent blank prepared similarly without adding PAM.

For DDQ method, into a series of 5 ml calibration flasks, different aliquots (0.25-4.0 ml) of standard 100 μg ml^{-1} PAM solution (equiv to 5-80 μg ml^{-1} PAM) were accurately transferred, and to each flask 1 ml of 0.2% DDQ solution was added and mixed. After 2 min, absorbance of red coloured CT complex was measured at 590 nm against the reference blank prepared similarly.

Standard graphs were prepared by plotting absorbance *vs* PAM concentrations, and the concentration of unknown was read from calibration graph or computed from respective regression equation derived using absorbance-concentration data.

Assay for Pharmaceutical Formulations

Tablets

Tablets (20) were weighed and pulverized. An amount of tablet powder (equiv to 25 mg PAM) was transferred into a 100 ml volumetric flask and 70 ml of acetonitrile was added to the flask. Content was shaken well for 20 min and diluted to the mark with the same solvent. Resulting solution was filtered through Whatmann No 42 filter paper and used for assay by following the general procedure described for CAA method. Resulting tablet extract (250 μg ml^{-1}) was diluted to 100 μg ml^{-1} with acetonitrile and suitable aliquot was used for assay in DDQ method.

Injections

Content of 10 injection ampoules were pooled and mixed together. One ml of Avil injection (equiv to 22.75 mg of PAM) was accurately measured and transferred into a 125 ml separating funnel. Water (20 ml) was added and solution was mixed well. pH of solution was raised to 9.5 by adding 1M NaOH and resulting pheniramine base was extracted with two 10 ml portions of chloroform. Resulted extracts were passed over anhydrous sodium sulphate and collected in a dry beaker. Solvent was evaporated on a water bath and resulting residue was dissolved in acetonitrile and volume was made up to the mark in a 50 ml volumetric flask with the same solvent. Resulting 455 μg ml^{-1} PAM solution was diluted appropriately to get 250 and 100 μgml^{-1} solutions with acetonitrile and used for assay in CAA and DDQ methods, respectively.

Procedure for Analysis of Placebo Blank and Synthetic Mixture

A placebo blank (starch, 10; acacia, 15; hydroxyl cellulose, 10; sodium citrate, 10; talc, 20; magnesium stearate, 15; and sodium alginate. 10 mg) was made and its solution was prepared as described under tablets. A synthetic mixture was separately prepared by adding pure PAM (40 mg) to placebo blank and mixture was homogenized. Extract was prepared by taking synthetic mixture containing PAM (25 mg in 100 ml) to give PAM (250 μg ml^{-1}) used in CAA method. Stock synthetic mixture extract was further diluted to 100 μg ml^{-1} and used for assay in DDQ method. Extracts containing three different concentrations of PAM were subjected to assay by following the general procedures and recovery% of PAM was evaluated.

Results and Discussion

CT complex forming reactions occur when π-acceptors react with basic nitrogenous compounds, acting

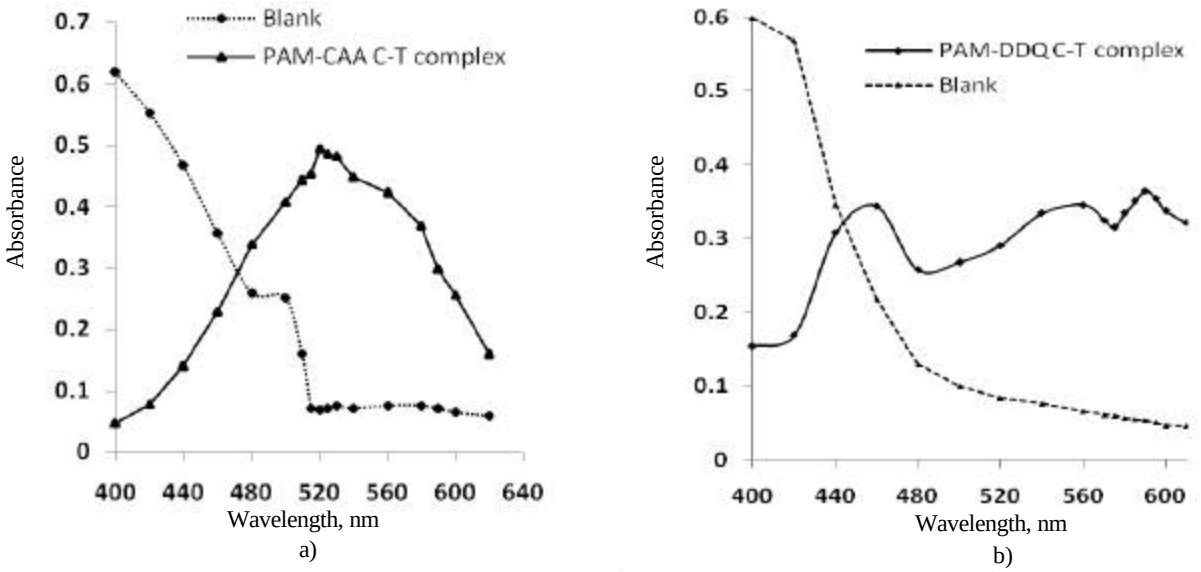


Fig. 2—Absorption spectra of: a) PAM-CAA (150 µg ml^{-1} PAM); and b) PAM-DDQ (40 µg ml^{-1} PAM) CT complexes

as n-donors. CT complex formation is characterized by electronic transition to an excited state, where transfer of electronic charge from donor to acceptor moiety takes place partially. Resonance in this excitation energy occurs very frequently in visible region of electro-magnetic spectrum[26]. This produces usually intense color characteristic for these complexes. Therefore, PAM, as n-donor, reacted with CAA and DDQ to produce a coloured CT complex in DAN solvent system. PAM reacts with π –acceptors (A) to form CT complexes of n–π type, which dissociate to give coloured free radical anions of acceptors as

$$PAM + A \rightleftharpoons \underset{\text{C-T complex}}{PAM\text{-}A} \rightleftharpoons PAM^{\cdot +} + A^{\bullet -}$$

Radical anion

In CAA method, PAM reacts with reagent and gives a red chromogen that exhibits a strong absorption maximum at 530 nm in DAN medium (Fig. 2a), attributed to formation of CT complex between PAM and CAA followed by formation of radical ions. This probably is due to dissociation of original (PAM-CAA) complex promoted by high ionizing power of acetonitrile solvent[27]. Whereas, interaction of PAM with DDQ in DAN at room temperature (RT) gave a red chromogen with three strong absorption maxima at 460, 550 and 590 nm due to the formation of free radical anion[28]. Wavelength 590 nm was selected for further studies because of higher sample absorbance and lower blank absorbance readings (Fig. 2b).

Optimization of Reaction Conditions

Optimum conditions were established by measuring absorbance of CT complexes at 530 for CAA and 590 nm for DDQ method by varying one parameter and keeping others constant.

Effect of Reagent Concentration

To establish optimum concentrations of reagents for rapid formation of stable CT complexes, PAM was allowed to react with different volumes of reagents (0.5-3 ml of 0.2% CAA or 0.5-3 ml of 0.2% DDQ). In both cases, maximum and minimum absorbance values were obtained for sample and blank, respectively, only when 1 ml of reagent was used. At higher volumes of reagents, the greater absorbance for blank and lower absorbance for CT complexes were observed. Therefore, 1 ml of reagent in a total volume of 5 ml was used throughout the study.

Effect of Solvent to Dissolve Drug and Reagents

Acetonitrile was preferred to dissolve PAM than dichloromethane, acetone, dichloroethane, 1,4-dioxan, methanol and ethanol because the complex formed in these solvents had very low absorbance values. Whereas in case of reagents, highly intense coloured products were formed when 1,4-dioxan medium was used as solvent to dissolve CAA and DDQ. Therefore, acetonitrile and 1,4-dioxan were chosen as solvents to dissolve PAM and the reagents, respectively.

Effect of Reaction Time and Stability of CT Complexes

Optimum reaction times were determined by measuring absorbance of formed complex upon addition of reagent solution to PAM solution at RT. In both methods, formation of CT complexation reaction was

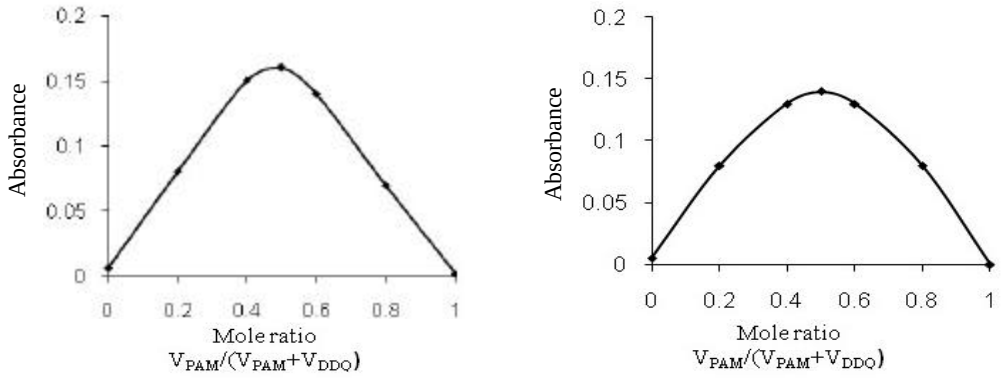
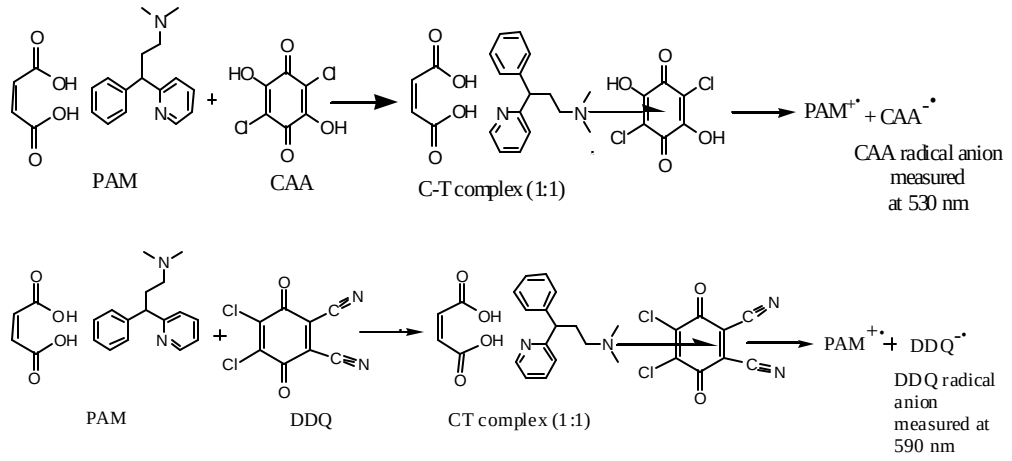


Fig. 3—Job's plots obtained for: a) 7.01× 10^{-4} M PAM and CAA CT complex; and b) 2.80 × 10^{-4} M PAM and DDQ CT complex



Scheme 1—Possible reaction pathway for the formation of CT complex between PAM and CAA/DDQ in DAN medium

instantaneous and absorbance values of PAM-CAA and PAM-DDQ complexes were stable for at least 3 h and 30 min, respectively.

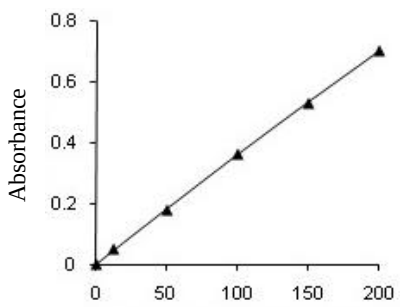
Investigation of Composition of CT Complexes

Composition of CT complexes of PAM with either CAA or DDQ was evaluated by following the Job's continuous variations method[29]. Experiments were performed by mixing equimolar solutions of drug and reagent [7.01 × 10^{-4} M (CAA method) and 2.80 × 10^{-4} M (DDQ method)] and by maintaining total volume at 5.0 ml. Plots of absorbance *vs* molar ratio between drug and reagent were prepared (Fig. 3), and results revealed that formation of CT complex between drug and reagent followed a 1:1 reaction stoichiometry. This finding was anticipated by the presence of one basic electron donating center (N atom) in PAM structure. Based on this fact, reaction pathway for formation of CT complex is proposed (scheme 1).

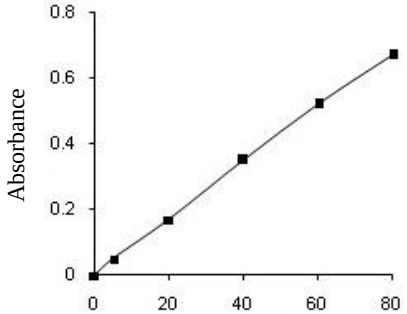
Validation of Methods

Linearity, Sensitivity, Limits of Detection and Quantification

A linear correlation was found between absorbance at λ_{max} and concentration of PAM (Fig. 4) under following sensitivity and regression parameters for CAA and DDQ method, respectively: λ_{max}, 530, 590 nm; Color stability, 3 h, 30 min; Linear range, 12.5-200, 5-80 µg ml^{-1}; Molar absorptivity(ε), 1.27 × 10^3, 3.06 × 10^3 l $mol^{-1}cm^{-1}$; Sandell sensitivity (Limit of determination as weight in µg per ml of solution, which corresponds to an absorbance of A = 0.001 measured in a cuvette of cross-sectional area 1 cm^2 and l = 1 cm), 0.2810, 0.1116 µg cm^{-2}; Limit of detection (LOD), 2.72, 0.82 µg ml^{-1}; Limit of quantification (LOQ), 8.25, 2.49 µg ml^{-1}; Regression equation Y (Y=a+bX, where Y is absorbance, X is



a)



b)

Fig.4—Calibration curves for: a) CAA method; and b) DDQ method

Table 1— Evaluation of intra-day and inter-day accuracy and precision

Method	PAM taken µg ml^{-1}	Intra-day accuracy and precision (n=7)			Inter-day accuracy and precision (n=5)		
		PAM found µg ml^{-1}	%RE	%RSD	PAM found µg ml^{-1}	%RE	%RSD
A	50	49.61	0.77	1.89	50.53	1.06	2.58
	100	101.52	1.52	0.88	101.9	1.86	1.64
	150	150.74	0.49	0.77	151.85	1.23	1.38
B	40	41.11	2.79	0.95	40.86	2.14	1.12
	60	61.19	1.99	1.04	38.59	2.35	2.46
	80	79.74	0.31	0.90	78.59	1.76	1.78

%RE: Percent relative error, %RSD: relative standard deviation, n = Number of measurements.

concentration in µg/ml), [Intercept (a), 0.0100, 0.0100], [Slope (b), 0.0035, 0.0084]; Standard deviation of b (S_b), 3.0×10^{-5}, 7.63×10^{-4}; and Regression coefficient (r), 0.9999, 0.9991. Regression analysis of Beer's law data using method of least squares was made to evaluate slope (b), intercept (a). Limits of detection (LOD) and quantitation (LOQ) calculated according to ICH guidelines[30] as LOD =3.3 S/b and LOQ = 10 S/b (where S is standard deviation of blank absorbance values, and b is slope of calibration plot).

Precision and Accuracy

Assays described under construction of calibration curves were repeated 7 times a day to determine intra-day precision and 5 times on different days to determine inter-day precision of the methods. These assays were performed at three levels of analyte. Percentage relative standard deviation (%RSD) values (≤ 1.8% intra-day and ≤ 2.58% inter-day) indicate high precision of the methods (Table 1). Accuracy was evaluated as percentage relative error (%RE) between measured mean concentrations and taken concentrations for PAM, calculated at each concentration. %RE values (≤ 2.35 %) demonstrate high accuracy of proposed methods.

Selectivity

Results obtained from placebo blank and synthetic mixture analyses revealed that inactive ingredients used in preparation did not interfere in the assay of active ingredient. Absorbance values from placebo blank solution were almost equal to the absorbance of blank, which revealed no interference from excepients. To study the role of additives added to tablets, 2 ml each of synthetic mixture solution (180 and 60 µg ml^{-1} in PAM from CAA and DDQ methods) was assayed (n=5). Recoveries [(96.7-103.6%) with RSD (0.86-2.11%)] demonstrated accuracy and precision of proposed methods and complement findings of placebo blank analysis with respect to selectivity.

Robustness and Ruggedness

Robustness of methods was evaluated by making small incremental changes in volume of reagent, and the

Table 2 —Method robustness and ruggedness expressed as intermediate precision (% RSD)

Method	PAM taken µg ml^{-1}	Robustness (%RSD)	Ruggedness	
			Inter-analysts (%RSD) (n=4)	Inter-instruments (%RSD) (n=4)
A	50	0.64	0.35	1.26
	100	0.86	0.48	1.78
	150	0.38	0.26	1.04
B	40	0.42	0.76	1.85
	60	0.58	0.48	1.26
	80	0.36	0.54	1.46

*The volumes of CAA or DDQ added were 1±0.2 ml

Table 3— Results of analysis of tablets and injection by proposed methods and statistical comparison of results with reference method

Formulation Name	Labeled amount*	Found# (% of label claim ± SD)		
		Reference method	CAA method	DDQ method
Avil-25	25	100.6±0.76	99.22±1.90 t = 1.64 F = 6.25	102.8±0.95 t =0.74 F =1.56
Avil-50	50	102±0.64	101.5±0.88 t = 1.66 F =1.89	101.9±1.05 t = 0.75 F =2.69
Avil injection	22.75	101±0.58	100.5±0.77 t = 2.10 F =1.76	99.68±0.90 t = 1.92 F =2.41

*Amount in mg per tablet and mg per ml in tablets and injection, respectively; #Mean value of 5 determinations; Tabulated t-value at 95% confidence level and for four degrees of freedom is 2.78; Tabulated F-value at 95% confidence level and for four degrees of freedom is 6.39.

Table 4— Results of recovery study *via* standard-addition method with tablet/injection

Tablets/ injection studied	CAA method				DDQ method			
	PAM in tablet µg ml^{-1}	Pure PAM added µg ml^{-1}	Total found µg ml^{-1}	Pure PAM recovered (Percent±SD*)	PAM in tablet µg ml^{-1}	Pure PAM added µg ml^{-1}	Total found µg ml^{-1}	Pure QTP recovered (Percent±SD*)
Avil-25	49.66	25.0	76.54	107.03±3.57	20.26	10.0	30.08	98.29±1.44
	49.66	50.0	101.02	102.72±1.88	20.26	20.0	40.15	99.49±2.28
	49.66	75.0	127.35	103.59±0.89	20.26	30.0	49.51	97.53±1.83
Avil injection	50.25	25.0	99.29	98.29±3.20	19.94	10.0	30.01	100.77±2.62
	50.25	50.0	101.36	101.36±2.26	19.94	20.0	40.15	101.08±1.12
	50.25	75.01	124.40	98.87±2.95	19.94	30.0	49.51	98.58±1.02

effect of changes was studied on absorbance of complex systems. Changes had negligible influence on results as revealed by small intermediate precision values (%RSD, ≤0.86%). Method ruggedness was demonstrated having analysis done by four analysts, and also by a single analyst performing analysis on four different instruments in same laboratory. Intermediate precision values (%RSD) in both instances were 0.26-1.85, indicating acceptable ruggedness (Table 2).

Application

Proposed methods were applied to quantification of PAM in commercially available Avil tablets (25 & 50 mg) and Avil injection (22.75 mg/ml PAM).

Results were compared with those obtained by a reference method[3], which involves potentiometric titration of PAM with 0.1 M perchloric acid in anhydrous acetic acid medium. Statistical analysis of results did not detect any significant difference in performance of proposed methods and reference method with respect to accuracy and precision as revealed by Student's t-value and variance ratio F-value [31] (Table 3).

Recovery Study

To further assess accuracy of proposed methods, recovery experiment was performed by applying standard-addition technique. Recovery was assessed by determining agreement between measured standard concentration and added known concentration to the sample. Test was done by spiking pre-analyzed tablet powder with pure PAM at three different levels (50, 100 and 150%) of the content present in tablet powder (taken) and total was found by proposed method. Each test was repeated three times. From this test, recovery values [(97.53-107.3%) with standard deviation (0.89-3.57%)] were close to 100%, indicating fairly good accuracy of methods (Table 4).

Conclusions

Two simple, extraction-free, rapid and cost-effective spectrophotometric methods based on CT complex formation reaction were developed and validated for determination of PAM. Reagents utilized in proposed methods are cheap, readily available, and the procedure does not involve any critical reaction conditions or tedious sample preparation. Most favorable features of proposed methods are their speed with high accuracy and simplicity unlike reported methods, which involve critical experimental conditions and tedious and time-consuming liquid-liquid extraction step. These methods can be used for determination of PAM in bulk powder, tablets and injection. Hence, methods can be used in routine analysis of drug in quality control laboratories.

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