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Spectrophotometric Determination of Some Phenothiazine Drugs in Pharmaceutical Preparations

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A sensitive spectrophotometric method has been developed for the assay of phenothiazine derivatives in bulk and their pharmaceutical preparations. The method is based on the formation of coloured species with p-benzoquinone in acid medium. The reaction involves oxidation of the phenothiazine nucleus into a semiquinonoid radical. The optimum reaction conditions and other analytical parameters are evaluated. The proposed method has been successfully applied to the analysis of the bulk drugs and their dosage forms, tablets and injections. No interference was observed from talc, dextrose or magnesium stearate in the proposed method. Statistical comparision of the results with those of an official method showed good agreement and indicated no significant difference in precision.

Phenothiazine derivatives make valuable pharmacological preparations. Owing to their versatile pharmacological actions, they are widely used in therapeutics, particularly as psychotropic drugs[1-3]. In view of their importance, considerable work has been done on their detection and quantification. Methods used for the determination of these drugs include titrimetry[4], fluorimetry[5], controlled-potential coulometry[6], gas liquid chromatography[7], polarography[8], spectrophotometry[1-3] and high performance liquid chromatography[9-10]. The official methods normally involve non-aqueous titrimetry or ultraviolet spectrophotometry[11-13]. The widespread use of these drugs has necessited the development of a rapid, simple and precise method for their routine quality control.

In this paper, a method of determination of four phenothiazine drugs such as chlorpromazine hydrochloride (CPH), promethazine hydrochloride (PMH), trifluoperazine dihydrochloride (TFPH) and prochlorperazine dimaleate (PPD) is described. This method is based on reaction of phenothiazines with p-benzoquinone in sulphuric acid to yield a red coloured product. This method has been applied to the assay of bulk and drugs in tablets, injections and syrups.

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EXPERIMENTAL

All spectral measurements were made on UV-Visible spectrophotometer model 150-20. Pharmaceutical grade (IP or BP) phenothiazines were obtained from various firms. Stock solutions of CPH, PMH, TFPH and PPD were prepared by dissolving requisite amount of the samples in distilled water and then standardised by cerium (IV) solution. Working solutions (100-3000 µg/ml) were prepared by appropriate dilution of the stock solutions with distilled water. A 0.05% (m/V) p-Benzoquinone (PBQ) was prepared in distilled water.

Assay procedure:

An aliquot of the sample solution containing 2.5-1300 µg of CPH, 3.0-750 µg of PMH, 2.5-1500 µg of TFPH or 2.5-1750 µg of PPD was transferred into 25 ml volumetric flasks. The acid concentration was adjusted to 4 M for CPH, 7 M for PMH, 6 M for TFPH and PPD with sulphuric acid. A 1.5 ml of 0.05% PBQ was added to

each flask and diluted to the mark with distilled water. The contents were mixed well and the absorbance was measured after 5-20 min at 525 nm for CPH, at 515 nm for PMH, at 500 nm for TFPH and at 527 nm for PPD against the corresponding reagent blank. A calibration graph was drawn or regression equation calculated.

A quantity of the sample (a mixture of 20 powdered tablets) equivalent to 25 mg of the drug was weighed accurately and transferred into a 100 ml volumetric flask and then volume made up with distilled water and filtered. Appropriate aliquots of the drug solution were taken and the standard procedure was followed for the analysis of drug content.

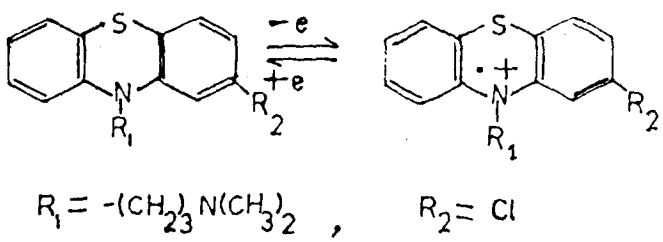
For the analysis of injections and syrups, the requisite volume was transferred to a 100 ml calibrated flask and diluted to the mark with distilled water. The phenothiazine content in the diluted solution was determined as described above.

RESULTS AND DISCUSSION

Phenothiazines undergo one electron reversible oxidation in acid medium to form red coloured species which is believed to be a radical cation[14] by PBQ. The probable mechanism of oxidation of CPH, a member of phenothiazines may be represented as shown in scheme 1.

The formation of radical cation was confirmed by the ion-exchange studies. The red coloured species was retained by cation-exchange resin but not retained on an anion-exchange resin column. The stability of the coloured species depends on the nature of the acid medium. The red species is unstable in hydrochloric acid and does not give maximum colour intensity in phosphoric acid or acetic acid medium. The maximum colour development is observed in 4 M sulphuric acid for CPH, 6 M for TFPH and PPD and 7 M for PMH. The maximum absorbance is obtained in 5-20 min. The effect of the concentration of PBQ was studied by measuring the absorbances at the specified wavelengths in the standard procedures for solutions containing a fixed concentration of phenothiazine and varying amounts of PBQ. A volume of 1.5 ml of 0.05% PBQ was necessary for maximum colour development for 0.1-70.0 µg/ml of phenothiazines. The order of addition of reagents had no effect on absorbance.

Scheme 1.



$R_1 = -(CH_2)_3N(CH_3)_2$, $R_2 = Cl$

Beer's law range, molar absorptivity Sandell's sensitivity, slope, intercept and correlation coefficient obtained by linear least-square treatment of the results are recorded in Table 1. Regression analysis of the Beer's law plots at λ_{max} reveal a good correlation (r=0.9966-0.9989). The graphs show negligible or zero intercept as

TABLE 1 : OPTICAL CHARACTERISTICS, PRECISION AND ACCURACY DATA

Parameter	CPH	PMH	PPD	TFPH
Beer's law limits (µg/ml)	0.1-52	0.12-30.0	0.1-70	0.1-30
Molar absorptivity ($l.mol^{-1}\ cm^{-1} \times 10^3$)	7.07	8.25	7.72	6.13
Sandell's sensitivity (µg cm^{-2}/0.001 Abs. unit)	0.05	0.038	0.077	0.078
Correlation coefficient, r	0.9974	0.9989	0.9973	0.9966
Slope, b	0.0166	0.026	0.0134	0.0121
Intercept, a	0.0483	0.0102	-0.0117	0.0176
Relative standard deviation (%)	1.23	1.42	0.94	1.16

TABLE 2 : EFFECT OF INTERFERRING IONS AND SUBSTANCES IN THE DETERMINATION OF 20 PPM OF PHENOTHIAZINES

Ions added	Tolerance limit (ppm)			
	CPH	PMH	PPD	TFPH
Chloride	1750	1400	1500	1800
Fluoride	800	680	875	1100
Bromide	30	50	65	35
Iodide	3	2	5	6
Oxalate	300	275	450	400
Sulphate	2000	1400	1100	1250
Citrate	400	600	450	250
Phosphate	1400	1650	1520	1600
Dextrose	8000	6500	9000	7800
Tartarate	250	300	450	400
Acetate	600	400	550	350
Alginate	280	350	320	220
Gum acacia	240	200	160	120

TABLE 3 : ASSAY OF PHENOTHIAZINES IN DOSAGE FORMS

Formulation	Labelled amount (mg/tablet or ml)	Amount Found (mg)		Mean Recovery* ± S.D% by Proposed method
		Proposed method	Reference method[3, 11-13]	
CPH				
Tablet 1	25	24.81	24.75	99.24±0.5
Tablet 2	50	49.63	49.12	99.26±0.7
Injection	25	25.12	24.72	100.48±0.4
PMH				
Tablet 1	10	9.95	9.98	99.5±0.4
Tablet 2	25	24.79	24.68	99.16±0.6
Injection	25	24.52	24.6	98.08±0.3
Syrup	0.5	0.5	0.51	100.0±0.5
PPD				
Tablet	5	4.95	5.03	99.0±0.5
Injection	12.5	12.43	12.49	99.44±0.4
TFPH				
Tablet 1	5.0	5.03	5.02	100.6±0.6
Tablet 2	10.0	9.90	9.98	99.0±0.2

* Mean and standard deviation of 5 determination

described by the regression equation, y=a+bx. The apparent molar absorptivities of the resulting coloured species range from 6.13 x 10^3 to 8.25 x 10^3 1 mol^{-1} cm^{-1} and indicate the high sensitivity of the proposed method.

In order to assess the possible analytical applications of the proposed method, the effect of some foreign ions which often accompany phenothiazines in pharmaceutical products were studied by adding different amounts of foreign ions to 20 ppm of phenothiazines. The colour was developed and the absorbance measured following the procedure described earlier. The tolerance limits of various substances causing an error of ±2.5% in absorbance values are given in Table 2. From the results it is evident that a large amounts of sulphate, dextrose, acetate and phosphate are tolerated. However, iodide and bromide ions interferred in the determinations. Thus the proposed method is free from positive or negative interferences by various substances and ions.

The proposed method was applied successfully for the determination of phenothiazines in pharmaceutical formulations. Results of the proposed method presented in Table 3 compare favourably with the official methods. This method is simple, rapid and offers the advantages of sensitivity and a wide range of determination without the need for extracting or heating. The commonly used additives and excipients such as talc, starch, magnesium stearate and dextrose do not interfere in the analysis.

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