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Extractive Spectrophotometric Determination of Phenothiazine Drugs with Chlorophenol Red

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A sensitive spectrophotometric method for the determination of chlorpromazine hydrochloride, promethazine hydrochloride, prochlorperazine maleate and trifluoperazine hydrochloride based on the formation of chloroform extractable complexes exhibiting maximum at 405 nm with chlorophenol red in acidic medium is described. A study of the effect of commonly associated excipients revealed that they did not interfere. Statistical analysis of the results indicates that the method is precise and accurate.

PHENOTHIAZINE drugs are used as antipsychotic, anticholinergic, antihistaminic and tranquilizers. Chlorpromazine hydrochloride (CPH), promethazine hydrochloride (PH), prochlorperazine maleate (PPM) and trifluoperazine hydrochloride (TFH) are official in B.P,[1] and U.S.P[2]. In view of their importance considerable work has been done for the determination of phenothiazine class of drugs as reviewed by Blazek **et al**[3] and Fairbrother.[4] Spectrophotometric[5,6], spectrofluorimetric,[7] polarographic[8] and chromatographic[9] methods are reported in the literature. The proposed extractive spectrophotometric method for the determination of phenothiazine drugs is based on the formation of complexes with chlorophenol red and these complexes are quantitatively extracted into chloroform. The developed procedure has been applied for the determination of trace amounts of phenothiazines in bulk drugs and dosage forms.

All spectral measurements were made on Shimadzu UV-150 spectrophotometer. Pharmaceutical grade phenothiazines were obtained from various firms. Stock solutions of CPH, PH, PPM and TFH were prepared by dissolving requisite amount of the samples in distilled water and then stadardised by cerium (IV) solution. Working solutions were prepared by appropriate dilution of the stock solutions with distilled water. Chlorophenol red was prepared in distilled water (0.1% W/V).

Table 1 : Optical characteristics of drug-chlorophenol red complexes in chloroform

Compound	Beer's law limits (μg/ml)	Molar absorptivity	Sandell's sensitivity	RSD (±)
Chlorpromazine HCl	2-13	19.6	0.016	1.3
Promethazine HCl	2-11	21.2	0.013	1.6
Trifluoperazine HCl	1-17	19.7	0.024	1.0
Prochlorperazine maleate	4-38	20.4	0.018	1.1

Sandell's sensitivity (μg/cm^2/0.001 absorbance unit); Molar absorptivity (dm^3 mol^{-1} cm^{-1} x 10^3)

Table 2 : Analysis of Phenothiazine drugs in formulations

Sample	mg/tab mg/ml	Found mg/tab or mg/ml by method		% Recovery*
		Proposed	Reported	
Promethazine HCl				
Tablet	25	24.60	24.68	99.5
Injection	25	24.71	24.60	100.6
Syrup	0.5	0.50	0.51	98.5
Chlorpromazine HCl				
Tablet	25	24.81	24.75	100.3
Injection	25	24.67	24.72	99.6
Syrup	5	4.93	4.9	100.8
Trifluoperazine HCl				
Tablet	5.0	5.06	5.02	100.9
Tablet	10.0	9.91	9.98	99.3
Prochlorperazine maleate				
Tablet	5.0	5.09	5.03	100.8

* Average of five determinations

Table 3 : Effect of interfering ions and substances in determination of 10 ppm Phenothiazines

Ion added	Tolerance limit, ppm			
	CPH	PH	TFH	PPM
Chloride	1500	1600	1400	1500
Nitrate	850	1000	970	900
Bromide	800	850	720	750
Sulphate	850	800	830	860
Acetate	400	300	280	375
Fluoride	300	175	200	250
Oxalate	250	300	350	350
Citrate	600	500	650	625
Ascorbic acid	4	6	3	4
Tartarate	1000	1100	950	1000

A suitable aliquot of CPH, PH, PPM or TFH solution was transferred into a series of 100 ml separating funnels and to each of these were added 1.0 ml of 5 N phosphoric acid and 1.5 ml of 0.1% chlorophenol red. Ten ml of chloroform was added to each funnel. The contents were shaken vigorously and left at room temperature for two minutes. The two phases were allowed to separate and the chloroform layer was passed through anhydrous sodium sulphate. Absorbance of the yellow coloured species was measured at 405 nm against a reagent blank. A calibration graph was plotted. The optical characteristics like Beer's law limits, molar absorptivity, Sandell's sensitivity for complexes are evaluated and recorded in Table 1.

The sample (pure drug, tablet powder) equivalent to 50 mg of the drug was transferred into a 100 ml volumetric flask and volume made with distilled water and solution filtered. Ten ml of filtrate was further diluted to 100 ml with distilled water. Appropriate aliquots of drug solution were taken and the procedure as under standard curve was followed. The amount of drug in the formulations was calculated from standard graph. For the analysis of injection and syrup, an appropriate amount of the sample is diluted with distilled water and analysed as above. Results are shown in Table 2.

To determine the accuracy and reproducibility of the above method, recovery experiments were performed using the method of additions. A fixed amount of pure sample was added to one of the three different concentrations of the standard drug solution. The total amount of drug was then determined using chlorophenol red and the amount of added drug found by difference. The extent of interference by common anions and substances was determined by measuring the absorbance of a solution containing 10 ppm of phenothiazines and various amounts of diverse ions. An error of ± 2.5% in the absorbance readings was considered tolerable. The substances tested and the tolerance limits found are presented in Table 3.

Phenothiazine drugs react with chlorophenol red in phosphoric acid medium to yield species which are extractable into chloroform. The yellow coloured complexes formed are very stable over a period of 10 h at room temperature. These complexes can be easily measured at 404-406 nm against a reagent blank. The effect of experimental variables have been thoroughly investigated. It is found that 0.5 - 1.5 ml of 5 N phosphoric acid and 0.75 - 2.0 ml of 0.1% chlorophenol red are suitable for maximum colour development. However, 1.0 ml of 5 N phosphoric acid and 1.5 ml of chlorophenol red are used in all subsequent work. The stability of the colour intensity is constant in the temperature range 15 - 40° for all drugs. It does not suffer any interference due to common excipients like talc, starch, stearic acid, sodium alginate, gelatin and dextrose. The proposed method is successfully applied for the analysis of phenothiazine drugs in various pharmaceutical preparations. The results of the assay of tablets, injection and syrup presented in Table 2 compare favourably with the official method of British pharmacopoeia.

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