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Spectrophotometric Determination of Phenothiazine Drugs with N-iodosuccinimide

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A simple and rapid spectrophotometric method for the determination of seven phenothiazine derivatives, based on the colour reaction with N-iodosuccinimide is described. The reaction proceeds *via* oxidation of phenothiazine nucleus into a semiquinonoid radical. The optimum reaction condition and other analytical parameters are evaluated. A study of the effect of commonly associated excipients revealed that they did not cause interference. The new method has been applied for the assay of phenothiazine drugs in pure and dosage form. Statistical comparison of the results with those of an official method shows excellent agreement and indicates no significant difference in precision.

INTRODUCTION

Phenothiazine derivatives are widely used as drugs in medical practice, especially in the treatment of psychiatric disorders. The other clinically useful properties of phenothiazine drugs include antihistaminics, antiemetics, analgesics and sedatives. During the last few years, interest in medical health and the continued introduction of new phenothiazine drugs have resulted in numerous publications on analysis of phenothiazines[1]. The methods used to assay to these drugs in bulk as well as in pharmaceutical preparations are titrimetry,[2] spectrophotometry[3–5], flow injection method[6], fluorimetry[7], coulometry[8], gas-liquid chromatography[9] and high performance liquid chromatogrphy[10]. The official methods of British Pharmacopoeia[11] and United States Pharmacopoeia[12] include non-aqueous titration for bulk drugs and an ultraviolet spectrophotometric method for dosage forms. The aim of the present work is to provide a simple spectrophotometric method for the assay of phenothiazines in formulations employing N-iodosuccinimide as a reagent.

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EXPERIMENTAL

Elico model CL-27 spectrophotometer with 1 cm-matched cells was used for spectral measurements.

Reagents: N-Iodosuccinimide (NIS): A freshly prepared 0.02% solution of N-iodosuccinimide (Aldrich Chemical Company Inc., USA) in distilled water containing a few drops of dilute hydrochloric acid. The solution was standardized iodometrically. All other chemicals were of analytical reagent grade.

Standard Solutions: Aqueous solutions of promethazine hydrochloride (PMH, Rhone-Poulenc Ltd., India), trifluopromazine hydrochloride (TPH, Sarabhai Chemicals, India), thioproperazine mesylate (TPPM, Rhone-Poulenc Ltd., India), trifluoperazine hydrochloride (TFPH, SmithKline Beecham, India), fluphenazine dihydrochloride (FPH, Sarabhai Chemicals), trimeprazine tartrate (TMT, Rhone-Poulenc Ltd.) and prochlorperazine maleate (PCPM, Rhone-Poulenc Ltd.) were prepared by dissolving the requisite amount of the samples in distilled water. Insoluble PCPM was dissolved by the addition of a few drops of dilute hydrochloric acid. Working solutions were prepared as required by dilution.

Standard procedure: An aliquot of sample solution containing 100–1000 μg of PMH, 75–1250 μg of TPPM, 100–750 μg of FPH, 50–750 μg of TFPH, 75–1125 μg of TPH, 125–1125 μg of PCPM or 25–750 μg of TMT were transferred into a series of 25 mL standard flasks. The acid concentration was adjusted to 6 M for PMH, FPH, TFPH, TPH and PCPM with hydrochloric acid and 2.5 M for TPPM, 2 M for TMT with sulphuric acid. A 2-mL volume of 0.02% NIS was added to each flask and the solutions were diluted to the mark with doubly distilled water. The solutions were mixed well and absorbance was measured at 515 nm for PHM, TPPM, and TMT, at 510 nm for FPH, TFPH and TPH, and at 530 nm for PCPM against reagent blank. The amount of phenothiazine was then deduced from the calibration curve.

Assay of Phenothiazine Drugs

Tablets: Twenty tablets (fifty tablets in the case of 1 mg TFPH/tablet) were weighed accurately and finely powdered in an agate mortar. An accurately weighed amount of the powder equivalent to 25 mg was transferred into a 100 mL standard flask and the volume made up with distilled water (the contents were thoroughly shaken for about 30 min) and filtered. Requisite amount of the drug solution was taken and the above standard procedure was followed for the assay of drug content.

Injection and elixir: The requisite volumes of injection and elixir solution were transferred into a 100 mL standard flask and diluted to the mark with distilled water. The phenothiazine content in diluted solution was determined as described above. The results of the analysis are given in Table-1.

TABLE-1
ASSAY OF PHENOTHIAZINE DRUGS IN COMMERCIAL PHARMACEUTICAL PREPARATIONS

Drug sample	Drug present	Label claim (mg)	Recovery (mg)	
			Official methods[11, 12]	Proposed method*
Tablets				
Phenergan[a]	PMH	25.00	24.52	24.8
Siquil[b]	TPH	10.00	9.98	9.90
Majeptil[a]	TPPM	5.00		4.98
Stemetil[a]	PCPM	5.00	5.08	4.95
Espazine[c]	TFPH	5.00	5.02	4.99
		1.00		0.98
Vallergan[a]	TMT	10.00		9.98
Injections				
Phenergan[a]	PMH	25.00	24.65	25.00
Siquil[b]	TPH	10.00	10.01	9.99
Stemetil[a]	PCPM	12.50	12.50	12.50
Espazine[c]	TFPH	1.00	0.99	1.05
Anatensol[b]	FPH	25.00	25.50	24.95
Elixir				
Phenergan[a]	PMH	1.00		0.97

* = Average recovery from six determinations
a = Marketed by Rhone-Poulenc Ltd., India
b = Marketed by Sarabhai Chemicals Ltd., India
c = Marketed by Pharmapak Ltd., India

RESULTS AND DISCUSSION

To optimize the procedure the influences of acid, reagent and other experimental conditions were investigated. Phenothiazines undergo one-electron reversible oxidation in acid medium to form a red intermediate, which is believed to be a radical cation[13]. This was confirmed by the ion-exchage technique.

Effect of acids: The sensitivity and stability of the coloured species depends on the nature and strength of the acid medium. The red species is not stable in phosphoric acid medium and does not give maximum colour intensity in acetic acid medium. The absorbance readings of the coloured species of PMH, FPH, TFPH, TPH and PCPM are maximum at 6 M hydrochloric acid and at 2.5 and 2.0 M sulphuric acid for TPPM and TMT, respectively.

Effects of NIS concentration: The effect of concentration of NIS was studied by measuring the absorbance at the specified wavelengths in the standard procedures for solutions containing a fixed concentration of phenothiazine and varying amounts of NIS. The constant absorbance readings obtained in the range

0.5–6, 0.5–7, 0.75–6, 0.5–5, 1.0–5, 0.5–6 and 1.0–5 mL of 0.02% NIS solution for PMH, TPPM, TFPH, FPH, PCPM, TPH and TMT, respectively. A volume of 2 mL of 0.02% NIS in a total volume of 25 mL was used in all subsequent work.

Effect of experimental variables: The time required for complete formation of the coloured species of phenothiazines with NIS was studied. The maximum colour was developed within 5 min for all phenothiazines after mixing the reactants. The maximum absorbance reading remained constant for a period of 50, 60, 30, 40, 35, 30 and 35 min for PMH, PCPM, TPH, TPPM, FPH, TFPH and TMT, respectively. The maximum colour intensity remained constant in the temperature range 5–40°C. The order of addition of reagents had no effect.

Linear least-square treatment: Precision studies were carried out for checking the reproducibility of the proposed method under standardized conditions. Good linearships were obtained over the concentration ranges; molar absorptivity and their corresponding Sandell's sensitivity are presented in Table-2. The slope, intercept and correlation coefficient obtained by a linear least-squares treatment of the results are also given in Table-2.

TABLE-2
OPTICAL CHARACTERISTICS AND PRECISION DATA

Parameters	PMH	TPPM	FPH	TFPH	PCPM	TMT	TPH
Beer's law limits (μg/mL)	4–40	3–50	4–30	2–30	5–45	1–30	3–45
Molar absorptivity ($\times 10^3$, L/mol/cm)	3.6	5.9	2.7	2.5	7.6	6.8	2.33
Sadell's sensitivity (μg/cm^2/0.001 abs.unit)	0.088	0.107	0.193	0.201	0.0803	0.0728	0.166
Regression equation (Y*)							
Slope (b)	0.0063	0.0105	0.00425	0.0054	0.0108	0.0149	0.0053
Intercept (a)	0.0565	–0.0228	0.00371	–0.0204	0.00226	–0.0147	–0.0125
Correlation coefficient (r)	0.99	0.98	0.99	0.998	0.9995	0.997	0.9985
% Relative standard deviation	0.98	0.93	1.2	1.35	0.91	0.89	1.4

Interference studies: To test the accuracy of the method, recovery experiments were performed on synthetic mixtures prepared in the laboratory. The usual tablet diluents and excipients such as talc, starch, dextrose, given acacia and gelatin were found not to interfere with the analysis by the proposed method and recoveries obtained were in the range 99.5 to 101%.

Application: The proposed method was successfully applied to the analysis of phenothiazine drugs in various commercial pharmaceutical preparations. The results of the assay of the tablets, injections and elixier presented in Table-1 compare favourably with official methods of the British Pharmacopoeia[11] and the United States Pharmacopoeia[12].

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