Spectrophotometric Determination of some Phenothiazine Drugs with Iodic acid

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A sensitive and accurate spectrophotometric method for the quantitative determination of four phenothiazine drugs in either pure form or in pharmaceutical formulation is proposed. The method is based on the development of a red or bluish-green coloured product with iodic acid in phosphoric acid medium. The reaction proceeds via oxidation of the phenothiazine nucleus into a semiquinonoid radical. The optimum reaction conditions and other analytical parameters are evaluated. The influence of substrates commonly employed as excipients with phenothiazine drugs has been studied. Results of analysis of pure drugs and their dosage forms by the proposed method are in good agreement with those of the official method.

Phenothiazines are widely used as antipsychotic, anticholinergic and antihistaminic drugs. In view of their importance, considerable work has been done for their detection and quantification. Many phenothiazine derivatives are official in British Pharmacopoeia and Indian Pharmacopoeia. The methods used for their determination include spectrophotometry[1,2] spectrofluorimetry[3], conductometry[4] and high performance liquid chromatography[5]. The official methods normally involve non-aqueous titrimetry or ultraviolet spectrophotometry[6,7]. The widespread use of these drugs has necessiated the development of a simple and sensitive method for their routine quality control.

In the present paper, a simple, accurate and sensitive spectrophotometric method for the determination of four phenothiazine drugs namely thioridazine hydrochloride (TDH), methdilazine hydrochloride (MDH), diethazine hydrochloride (DH) and propericiazine (PPC) using iodic acid in phosphoric acid medium is described. The method is based on the interaction of phenothiazines with iodic acid to yield a red or bluish-green coloured product. The method has been successfully applied to the assay of these drugs in pharmaceutical preparations.

A Hitachi UV-visible spectrophotometer model 150-20 with 1 cm matched quartz cell was used for all absorbance measurements. All chemicals used were of analytical reagent grade. A 1% iodic acid was prepared in distilled water. Aqueous solutions of diethazine hydrochloride (Leciva, zechosolvakia), thioridazine hydrochloride (Torrent, Vatva) and methdilazine hydrochloride (Glaxo India, Thane) were prepared by dissolving accurately weighed amount of phenothiazines (100 mg each) in distilled water and diluted to 100 ml. Insoluble propericiazine (Bayer A.G., Leverkusen) was dissolved by adding a few drops of dilute sulphuric acid and diluted to 100 ml with distilled water. Working solutions were prepared as required by dilution.

An aliquot of the sample solution containing 5-310 µg of MDH, 6-300 µg of TDH, 5-300 µg of DH or 6-320 µg of PPC was transferred into a series of 10 ml volumetric flasks. The acid concentration was adjusted to 4 M for DH, 1 M for TDH and 3 M for both MDH and PPC with orthophosphoric acid. Two millilitres of 1% iodic acid was added to each flask containing DH, MDH and PPC and 1ml of iodic acid was added to the flasks containing TDH. The contents were diluted to 10 ml with distilled water and mixed well. The absorbance was measured at 512 nm for MDH, at 510 nm for PPC, at 515 nm for DH and at 637 nm for TDH against the corresponding reagent blank.

Synthetic mixtures with the compositions given in Table 1 were prepared by adding all the excipients together. The mixture was powdered and mixed well. A portion of the mixture containing about 25 mg of MDH, TDH,

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TABLE 1: RECOVERY OF PHENOTHIAZINES FROM VARIOUS EXCIPIENTS

Drug	Amount present (mg)	Excipients, mg						Recovery*, %	RSD
		Talc	Lactose	Starch	Gelatin	Sucrose	Magnesium stearate		
MDH	50	150	200	250	50	200	100	98.9	1.2
TDH	100	200	150	200	50	150	75	99.2	1.1
DH	120	250	200	175	50	200	100	101.1	1.4
PPC	125	250	250	200	50	100	100	99.1	0.9

*Average recovery from five determinations. The analysis was carried out by the method reported in the present investigation.

DH or PPC was accurately weighed, transferred into a 100 ml volumetric flask and diluted with distilled water. It was shaken well and filtered. An appropriate aliquot of the solution was taken and the standard procedure was followed for the analysis of drug content and the results are presented in Table 1.

Commercially available tablets (20) containing MDH, TDH or DH were weighed and powdered. An accurately weighed portion or the powder equivalent of 25 mg of the drug was transferred into a 100 ml volumetric flask and diluted to volume with distilled water. Using a mechanical stirrer the powder was completely disintegrated and the solution filtered. An aliquot of this solution was taken and the standard procedure was followed for the analysis of drug content. The results of analysis are given in Table 2.

For the analysis of syrups the requisite volume was diluted to 100 ml with distilled water. Phenothiazine drug

TABLE 2: ANALYSIS OF PHENOTHIAZINE FORMULATIONS

Phenothiazine Drug	Label claim (mg/tablet)	Amount found Official# method (mg)	Proposed method	Recovery* ±SD % by proposed method
MDH				
Tablet 1	8.0	7.88	7.90	99.82±0.7
Tablet 2	10.0	9.94	9.98	98.99±0.5
Syrup 1	4.0/5ml	3.98	3.99	99.16±0.3
Syrup 2	8.0/5ml	7.95	7.98	99.31±0.4
TDH				
Tablet 1	25.0	24.71	24.82	98.82±0.4
Tablet 2	100.0	98.86	98.93	99.19±0.3
DH				
Tablet 1	10.0	9.99	9.93	99.13±0.2
Tablet 2	25.0	24.5	24.69	98.85±0.4

*Average of five determinations. Determination of MDH, TDH and DH in pharmaceutical preparations using the current method. #British Pharmacopoeia, HMSO, London, 1980 and 1993.

content in the solution was determined as described above using a suitable volume of aliquot and the results are recorded in Table 2.

Phenothiazines undergo one-electron reversible oxidation in acid medium to form a red or bluish-green species, which is believed to be a radical cation[8]. This was confirmed by ion-exchange technique. The red or bluish-green coloured species was retained by cation-exchange resin but not on an anion-exchange resin. The stability of the coloured species depends on the nature of acid medium. The red or bluish-green coloured species is unstable in hydrochloric acid medium and does not give more intense colour in acetic acid medium. The maximum colour intensity development was obtained in the range of 2-4 M for MDH and PPC, 3-5 M for DH and 1-2 M orthophosphoric acid for TDH. Hence, 4 M, 1 M and 3 M orthophosphoric acid for DH, TDH and for MDH and PPC were maintained respectively in subsequent studies. The maximum absorbance was obtained immediately and remained constant for a period of 10-15 min.

The effect of the concentration of iodic acid 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 iodic acid. The constant absorbance readings were obtained in the range of 1-5 ml of 1% iodic acid solution for DH, MDH and PPC. However, a volume of 2 ml of iodic acid in a total volume of 10 ml was used for the analysis of DH, MDH and PPC, while constant absorbance was observed with 1 ml of iodic acid for TDH.

The maximum colour intensity remained constant in the temperature range of 10-35°. The order of addition of reagents had no effect on absorbance. Beer's law range, molar absorptivity, slope, intercept and correlation coefficient obtained by linear least squares treatment of the results are presented in Table 3.

The extent of interference by commonly associated excipients such as magnesium stearate, starch, talc, gelatin, dextrose, lactose and sucrose was determined by measuring the absorbance of a solution containing 20 ppm of phenothiazine. An error of ±2.0% in the absorbance readings was considered tolerable. The proposed method was found to be free from interferences by the excipients. In order to test the accuracy of the method, recovery experiments were performed on synthetic mixtures prepared in the laboratory and the results of analysis are given in Table 1.

The method developed in this study was successfully applied to the analysis of phenothiazine drugs in

TABLE 3: OPTICAL CHARACTERISTICS AND PRECISION DATA

Parameter	DH	MDH	TDH	PPC
λ_{max} (nm)	515	512	637	510
Beer's law limits (µg/ml)	0.5-30	0.5-31	0.6-30	0.6-32
Molar absorptivity ($l\ mol^{-1}\ cm^{-1} \times 10^3$)	6.71	6.83	6.146	6.846
Sandell's sensitivity ($\mu g cm^{-2}$/0.001 Abs. Unit)	0.0444	0.04338	0.0662	0.05338
Correlation coefficient, r	0.9988	0.9989	0.9992	0.9981
Regression equation (Y)				
Slope, b	0.02622	0.02257	0.014278	0.022562
Intercept, a	-0.076504	-0.002115	-0.007167	-0.08496
Relative Standard Deviation* (%)	0.93	1.12	1.06	1.02

*Average of five determinations.

tablets and syrups. The content of the phenothiazine drug was calculated using the formula:

$$\text{mg. phenothiazine} = \frac{A_t.D.C.}{A_s.100}$$

where A_t and A_s are the absorbances of the test and the standard solutions respectively, C is the concentration of phenothiazine in $\mu g\ ml^{-1}$ and D is the dilution factor.

The proposed method is simple and offers the advantage of sensitivity and a wide range of determination without the need for heating or extraction. Moreover the proposed method does not involve any critical reaction conditions or overall tedious sample preparation. Hence the proposed method may be utilized for routine quality control of phenothiazine drugs.

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Salubrious Effect of *Tridax procumbens* on Paracetamol Hepatotoxicity

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***Tridax procumbens* is a hepatoprotective agent. Overdosage of paracetamol induces hepatotoxicity. This paper reports the salubrious effect of *Tridax procumbens* on the paracetamol-induced hepatotoxicity in Wister rats.**

Paracetamol (Acetaminophen) is an analgesic and antipyretic which is considered safe when taken appropriately. It is marketed under various brand names[1]. Since it is available without prescription, it has earned a prominent place as a common household analgesic. Overdose of paracetamol causes hepatic necrosis in laboratory animals[2] and in men[3]. Paracetamol is metabolised primarily by the hepatic microsomal enzymes[4]. After therapeutic doses, 90-100% of the drug may be recovered in the urine, primarily after hepatic conjugation with glucuronic acid and sulfuric acid[5]. A portion of paracetamol undergoes cytochrome P_{450}-mediated N-hydroxylation to form a highly reactive intermediary metabolite. This metabolite conjugates with glutathione to form a non-toxic mercapturic acid. In overdoses, the availability of glutathione was decreased to conjugate with the metabolite and so the unconjugated metabolite induces the liver cell necrosis[6].

Tridax procumbens belongs to the family Asteraceae of dicotyledons. It is a common weed found in varied ecological habitats. *Tridax* has been used by the village folk to cure cuts and wounds. Udupa *et al.*[7] studied the effect of *Tridax* on the developing granulation tissue in

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