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Four simple procedures for the assay of methdilazine in bulk drug and in tablets and syrup using potassium iodate

K. Basavaiah *, V.-S. Charan

Department of Chemistry, University of Mysore, Manasagangothri, Mysore 570 006, Karnataka, India

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Abstract

Four simple, selective, accurate and reproducible procedures are described for the assay of methdilazine in bulk form and in formulations. One titrimetric and three spectrophotometric methods are based on the oxidation of the drug with potassium iodate, and determination of either excess iodate or iodine released in the reaction. In the titrimetric method (Method A) the drug is reacted with a known excess of iodate in sulphuric acid medium followed by the iodometric determination of residual oxidant. The residual oxidant is determined by reacting it with variamine blue and measuring the absorbance of the oxidised dye at 540 nm (Method B). The second spectrophotometric method (Method C) is based on the oxidation of the drug in sulphuric acid medium in the presence of chloride ions by a large excess of iodate and the iodate being reduced to iodine. The ICl_2^- generated in this reaction is used to iodinate 2′,7′-dichlorofluorescein dye, and the red colour of the iodinated dye is measured at 525 nm. The other spectrophotometric method (Method D) also involves the oxidation of the drug in acid medium by a large excess of iodate with the liberation of iodine and its subsequent extraction with carbon tetrachloride followed by measuring the absorbance 520 nm. The methods were successfully applied to the determination of methdilazine in tablets and syrup and the results obtained in agreement with the label claim.
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Keywords: Methdilazine determination; Titrimetry; Spectrophotometry; Variamine blue; Dichlorofluorescein; Formulations

1. Introduction

Methdilazine hydrochloride (MDH) belongs to phenothiazine class of drugs. Medicinally, MDH has been used as an antihistamine and it is also found to possess antipruritic action [1]. Quantitation of MDH has been achieved by reversed phase and ion-exchange electrochromatography [2] and high performance liquid chromatography [3], and separation by thin layer chromotography [4]. But the equipment required is not always widely available. Moreover, procedures involve complicated and time consuming sample pretreatment. The spectrophotometric determination of the drug has been carried out by various procedures based on redox property and complex formation or coupling ability of the drug. Several oxidants like iron (III), persulphate and hypochlorite in combination with 3-methylbenzothiazolin-2-one hydrazone (MBTH) have been used to determine microquantities of methdilazine in pharmaceuticals [5]. But the procedures lack selectivity. The red coloured radical cation formed when the drug was heated with sodium cobaltinitrite [6], and iodic acid [7] in strong phosphoric acid medium has served as a basis for its assay in parts per million levels. Hematin formed insitu from haematoxylin and chloramine-T in phosphate buffer solution of pH 7.0 was made to react with methdilazine at 70 °C to form a complex that could be measured at 555 nm. This reaction scheme was used by Sastry et al. [8] for the determination of 100–800 μg of the drug. The procedure, besides requiring heating, lacks sensitivity. The same authors have suggested a routine control procedure based on the extraction of methdilazine–cobalt thiocyanate ion-associate complex [9] into chloroform and measurement at 620 nm. However, the procedure is less sensitive with the Beer's law range being 50–500 μg ml^{-1}. Another spectrophotometric method that utilises an uncharacterised

* Corresponding author.
E-mail address: basavaiahk@yahoo.co.in (K. Basavaiah).

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chromogen [10] formed when methdilazine was reacted with dapsone and persulphate in alkaline medium has also been reported by the same authors. Methdilazine hydrochloride is reported to react with Van Urk reagent in the presence of little iron (III) chloride to form a complex with an absorption maximum at 515 nm, forming the basis for the assay of drug in tablets and syrups.

The present investigation was undertaken with the aim of developing new, simple, rapid and accurate methods free from many of the drawbacks usually encountered in methods reported earlier, for the analysis of methdilazine.

2. Experimental

2.1. Apparatus

A Systronics model 106 digital spectrophotometer with 1 cm matched glass cells was used for absorbance measurements.

2.2. Reagents and solutions

All the reagents used were of analytical grade. Doubly distilled water was used throughout the work. A 0.002 M potassium iodate solution was prepared by dissolving 0.107 g of reagent (Sarabhai M. Chemicals) in water and diluting to 250 ml in a standard flask. Sodium thiosulphate solution (0.012 M) was prepared by dissolving 2.97 g of the reagent in water and diluting to 1 l and standardised [11]. Sulphuric acid (10 M) was prepared by adding 558 ml of concentrated acid (s.d. Fine Chem. India) Sp. gr.1.83, to 442 ml of water with cooling. This was diluted stepwise to get 1 N acid. Potassium iodide (10%) and starch indicator were prepared in the usual way and used for titrimetric work. Potassium iodate solutions (2; 0.4% and 50 μg ml^{-1}) were prepared by dissolving requisite amounts of the reagent in water and diluting to definite volumes. A 1 N sodium acetate solution was prepared by dissolving 8.4 g of reagent (Ranbaxy Chemicals) in water and diluting to 100 ml. Variamine blue (0.1%) was prepared by dissolving 100 mg of dye in 10 ml of methanol and diluting to 100 ml with water and filtered. A 0.01% dichlorofluorescein was prepared by dissolving 25 mg of reagent (May and Baker Ltd., UK) in 0.5 ml of 1 N sodium hydroxide and diluting to 250 ml with water. Sodium chloride solution (6%) was prepared by dissolving 6 g of reagent in 100 ml of water. Monochloroacetic acid reagent was prepared by dissolving 19 g of reagent (s.d. Fine Chem.) in 30 ml of water and mixing with a solution of sodium hydroxide containing 8 g in 30 ml. and diluting to 100 ml with water. The pH of this reagent was found to be 4.35 and used for Method C. The pH of this reagent was adjusted to 3.0 by adding hydrochloric acid and used for Method B. Spectroscopic grade carbon tetrachloride (Qualigens) was used for Method D.

2.2.1. Standard drug solution

Pharmaceutical grade methdilazine hydrochloride was kindly gifted by Glaxo Allenburgs Ltd., India and was used as received. A stock standard solution containing 2000 μg ml^{-1} of the drug was prepared by dissolving 200 mg of the sample in water and diluting to 100 ml in a standard flask. The solution was kept in amber coloured bottle and stored in a refrigerator. Working solutions of 50, 200 and 1000 μg ml^{-1} for Method B, Method C and Method D, respectively, were prepared by appropriate dilution of the stock solution whenever required.

2.3. Procedures

2.3.1. Method A

A 10 ml aliquot of the drug solution containing 2–18 mg of methdilazine hydrochloride was transferred into a 100 ml titration flask and made acidic by adding 1 ml of 10 M sulphuric acid. Then, 10 ml of 0.002 M potassium iodate solution was added by means of a pipette, the contents were mixed well. The flask was kept aside for 20 min with occasional shaking to facilitate the oxidation of the drug as indicated by the disappearance of the red colour of the radical cation. Then, 5 ml of 10% potassium iodide solution was added and the liberated iodine was titrated with thiosulphate (0.012 M) using 0.5 ml of starch indicator. A blank was sun in the same way with 10 ml of water. The drug content was calculated from:

$$\text{mg drug} = \frac{(B - S)MW}{n}$$

where B, volume of thiosulphate consumed in the blank titration; S, volume of thiosulphate consumed in the sample titration; W, molecular weight of the drug; M, molarity of potassium iodate solution; n, number of mol of iodate reacting with 1 mol of drug.

2.3.2. Method B

In to a series of 10 ml calibrated tubes were transferred 0, 0.25, 0.50...2.0 ml of 50 μg ml^{-1} of methdilazine hydrochloride solution by means of a microburette followed by 0.5 ml of 1 N sulphuric acid and 1 ml of 50 μg ml^{-1} potassium iodate. The volume was adjusted to 4 ml by adding requisite volume of water and kept in a boiling water bath for 15 min. When the oxidation of the drug was complete as indicated by the disappearance of the red colour, the tubes were cooled to room temperature (r.t.) and 0.5 ml of 1 N sodium acetate, 2 ml of 10% potassium iodide were added and let stand for 2 min before adding 1 ml of

0.1% variamine blue dye solution. The volume was diluted to mark with water and absorbance was measured at 540 nm against water.

2.3.3. Method C

Aliquots (0.25–3.00 ml of 200 μg ml^{-1}) of standard methdilazine hydrochloride solution were taken in a series of 10 ml standard flasks. To each of these flasks, 0.5 ml of 1 N sulphuric acid, 1 ml of 0.4% potassium iodate and 0.5 ml of 6% sodium chloride were added and kept aside at r.t. till decolouration, with occasional shaking. Two millilitre each of 0.01% dichlorofluorescein dye and chloroacetic acid reagent of pH 4.35 were added and the volume was diluted to the mark with water. The absorbance of the coloured solution was measured at 525 nm after 5 min against the reagent blank.

2.3.4. Method D

Different portions, varying from 0.5 to 6.0 ml of 1000 μg ml^{-1} of methdilazine hydrochloride solution were buretted into different 125 ml separating funnels. Then, 3 ml of 1 M sulphuric acid and 1 ml of 2% potassium iodate solution were added to each funnel and the volume was adjusted to 15 ml by adding water, mixed well and let stand for 15 min with occasional shaking to allow the oxidation of the drug to complete as indicated by the disappearance of the red colour. Five millilitre of carbon tetrachloride were added to each funnel and shaken for 2 min. The organic layer was separated, dried over anhydrous sodium sulphate and absorbance measured at 520 nm against the reagent blank.

In all the three spectrophotometric methods, calibration graphs were constructed by plotting the absorbance against concentration of drug. The concentration of the unknown was read from the respective calibration graph or calculated using the regression equation.

2.3.5. Determination of drug in formulations

2.3.5.1. Tablets. Twenty five diloysin tablets were finely ground and the entire mass was quantitatively transferred into a 100 ml standard flask, 60 ml of water added and shaken thoroughly for about 20 min. Then, the volume was made up to the mark with water, mixed well and filtered using a quantitative filter paper. First 10 ml of the filtrate was rejected and a suitable aliquot was used for assay by titrimetry. The tablet extract was diluted to get 50, 200 and 1000 μg ml^{-1} of the drug for spectrophotometric procedures B, C and D, respectively, and proceeded as described under procedures.

2.3.5.2. Syrup. The contents of the bottle (115 ml) were quantitatively transferred into a 250 ml separating funnel. The bottle was washed with 20 ml of water and the washings were also transferred into the separator. The contents were rendered alkaline to litmus paper with 6 N ammonia solution and 1 ml in excess was added. The mixture was then extracted with 3×20 ml portions of chloroform, the chloroform extracts were evaporated to dryness on a steam bath and the residue was dissolved in 0.1 N hydrochloric acid and made up to 100 ml with water. An aliquot of this solution containing 0.92 mg ml^{-1} of the drug was used for titrimetric analysis (Method A) and spectrophotometric assay (Method D). However, for method B and method C, the solution was diluted to 50 and 200 μg ml^{-1}, respectively, and assayed using a convenient aliquot.

3. Results and discussion

Methdilazine hydrochloride being a N-substituted phenothiazine derivative (Fig. 1) is oxidised first to a red coloured radical cation and finally to colourless sulphoxide [12] by iodate in sulphuric acid medium, and iodate in turn gets reduced to iodine. In the first two methods (A and B) the drug is reacted with a known excess of iodate, and after oxidation, the residual iodate is determined by iodometric titration (A) and by spectrophotometry (B) using variamine blue dye. The latter two methods rely on the determination of iodine formed in the redox process using an auxiliary reaction involving dichlorofluoresceim (C) and by extracting iodine to CCl_4 and measuring at 520 nm (D).

3.1. Optimisation of experimental variables

3.1.1. Method A

Potassium iodate was found to react quantitatively with methdilazine in sulphuric acid medium. One ml of 10 M acid in a total volume of 25 ml was found adequate, though 0.5–2.5 ml resulted in the same value of '*n*'. Stoichiometric study revealed that 3 mol of methdilazine reacted with 1 mol of potassium iodate in conformity with the reaction scheme given in Fig. 2. The reaction stoichiometry indicates that only S-atom of the drug was oxidised and other sites of the molecule were unaffected. For the 2–18 mg range studied, a 10 ml volume of 0.002 M iodate solution was found adequate for the complete oxidation of the drug. Though the oxidation of methdilazine was complete in 15 min,

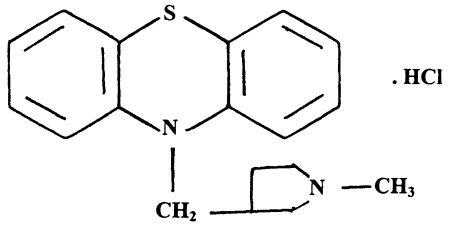

Fig. 1. Structure of methdilazine hydrochloride (MDH).

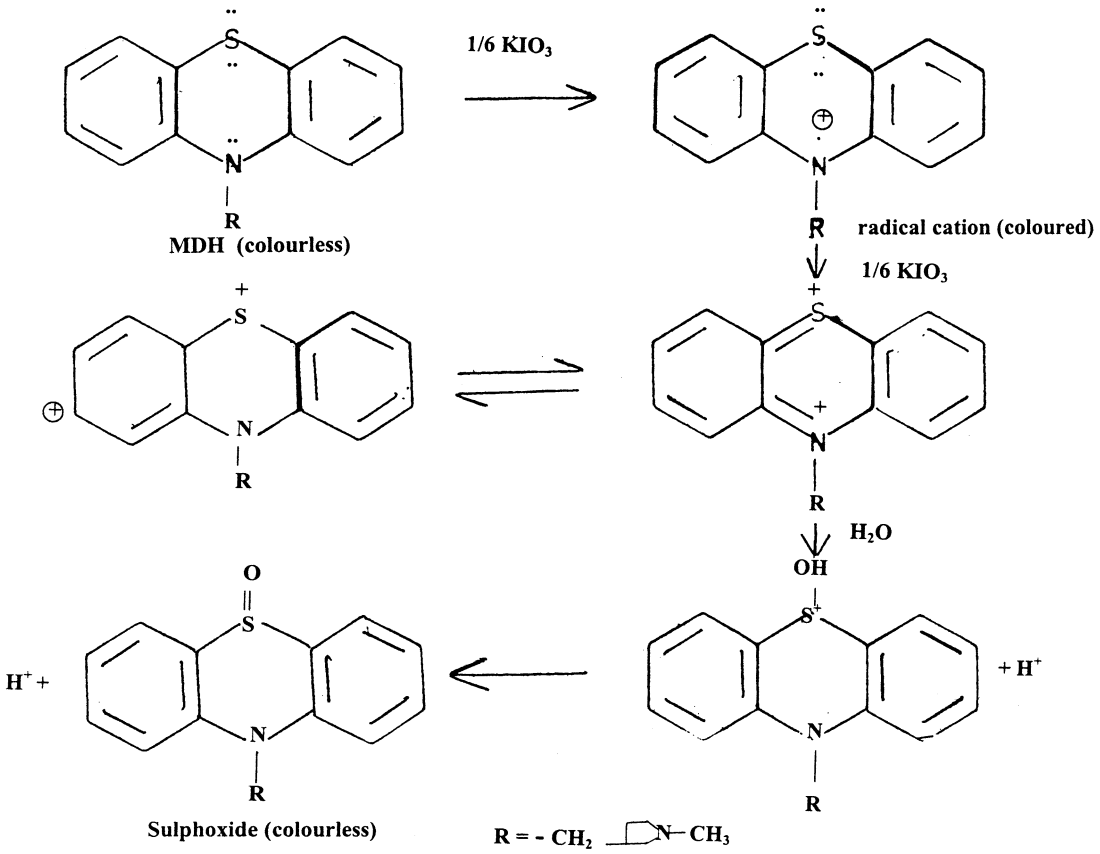

Fig. 2. Oxidation scheme for MDH by iodate.

contact times upto 2 h had no effect on either the stoichiometry or the results. The relation between the titration end-point and the drug amount was examined. The linearity between the amount of drug and the titration end-point is apparent from the correlation coefficient of 0.9968 suggesting that the reaction between methdilazine and iodate proceeds stoichiometrically in the ratio 3:1.

3.1.2. Method B

Oxidation of methdilazine (12.5–87.5 μg) by iodate (50 μg) at the acid concentration employed was slow at ambient temperature and was complete when the reactants were heated in a boiling water bath for 15 min. This step also helped to remove traces of iodine released during the redox process which otherwise would have resulted in negative error since the method essentially involves the determination of unreacted iodate iodometrically. Though iodine is reported to react with variamine blue at pH 0–5 [13] to form a pink coloured chromogen, maximum sensitivity was obtained at pH 3 which was achieved by adding 0.5 ml of 1 N sodium acetate followed by 2 ml of monochloroacetic acid agent (pH 3) prior to the addition of variamine blue. One ml of 0.1% variamine blue was adequate to react quantitatively with iodine produced by the action of potassium iodide on the residual iodate, the latter reaction being complete when 2 ml of 10% iodide solution were used. The colour formation was instantaneous and thereafter remained stable for 30 min.

Methdilazine, when added in increasing amounts, consumes iodate; consequently there is a concomitant fall in iodate concentration. This is observed as a proportional decrease in the absorbance of the chromogen on increasing the amount of the drug. Two blanks were prepared for this system. The reagent blank, which contained optimum concentrations of all the reactants except methdilazine, gave maximum absorbance (Fig. 3). The other blank was prepared in the absence of iodate to determine the contribution of other reactants to the absorbance of the system. Since the second blank had negligible absorbance at 540 nm, the absorbance of the developed colour was measured against water. The decreasing absorbance values at 540 nm were plotted against increasing concentrations of methdilazine to obtain the calibration graph.

3.1.3. Method C

Several substances of pharmaceutical interest [14–21] have been determined by measuring the iodine released in the redox reaction between the substrates and iodate in acid medium. In the present investigation, we have

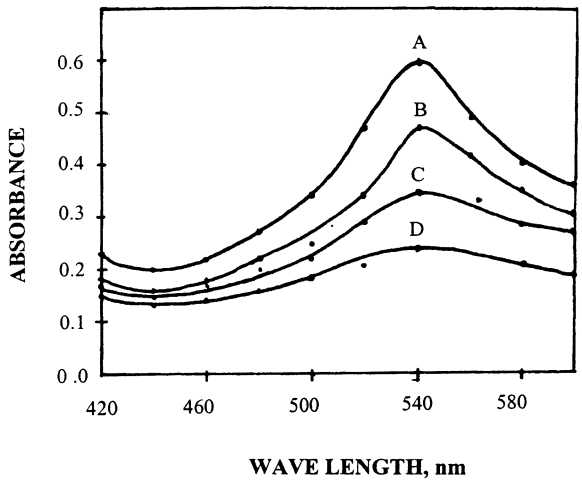

Fig. 3. Absorption spectra of the coloured species used in Method B. **A** = Blank; **B** = 2.5 μg ml^{-1} of MDH, **C** = 5.0 μg ml^{-1} of MDH, **D** = 7.5 μg ml^{-1} of MDH.

used a novel reaction for the determination of iodine released in the process, through iodination of dichlorofluorescein dye and measurement of the iodidanated dye at 525 nm. In this procedure, oxidation of methdilazine is effected by a large excess of iodate (1 ml of 0.4%) in the presence of 0.5 ml of 1 N sulphuric acid at ambient temperature, and the oxidation of the drug to colourless sulphoxide was complete in 15 min. The liberated iodine was further oxidised by excess iodate in the presence of chloride ions (0.5 ml of 6%) as ICl_2^-. This species is a better iodinating agent than iodine and was used to iodinate 2′,7′-dichlorofluorescein to yield 2′,7′-dichloro 4′,5′-diiodofluorescein (Fig. 4). A 2 ml of 0.01% dye solution was found sufficient for this reaction.

In order to observe a distinct variation of colour between dichlorofluorescein and the iodinated dye, the pH of the medium was varied using different buffer systems. The maximum colour intensity with a desired low-blank absorption was observed at 525 nm in the pH range of 3.25 ± 0.1. At this pH the iodinated dye is stable for more than 18 h. This pH could be maintained by the addition of 2.0 ml of monochloroacetic agent (pH 4.35).

3.1.4. Method D

The measured absorbance of iodine, extracted into carbon tetrachloride, formed due to reduction of iodate on its reaction with methdilazine in sulphuric acid medium, was found to be proportional to the concentration of drug. Several parameters involved in the redox reaction and subsequent measurement of iodine released, like the concentration of various reagents, reaction time, shaking time, number of extractions and choice of solvent for extraction, were optimised. A 3 ml volume of 1 M sulphuric acid in a total volume of 15 ml was found adequate for the oxidation of methdilazine to its sulphoxide which will be complete in 15 min as indicated by the disappearance of the red colour due to the radical cation. A large excess (1 ml of 2%) of iodate was used to facilitate the redox reaction in a reasonable time indicated above. A single extraction with 5 ml of carbon tetrachloride was sufficient to extract the iodine produced. The extent of extraction was found to be constant with times of shaking from 0.5 to 3 min. For convenience, 1 min was chosen for the standard procedure. Different aqueous to organic phase ratios like 1:1, 2:1 or 3:1 had no effect in the extractability of iodine. A ratio of 2:1 was used in the investigation. The separation of two phases was quick, however, 2 min separation time was allowed before removing the organic layer. Of the several organic solvents tried, like cychlohexane, carbon tetrachloride, chloroform and

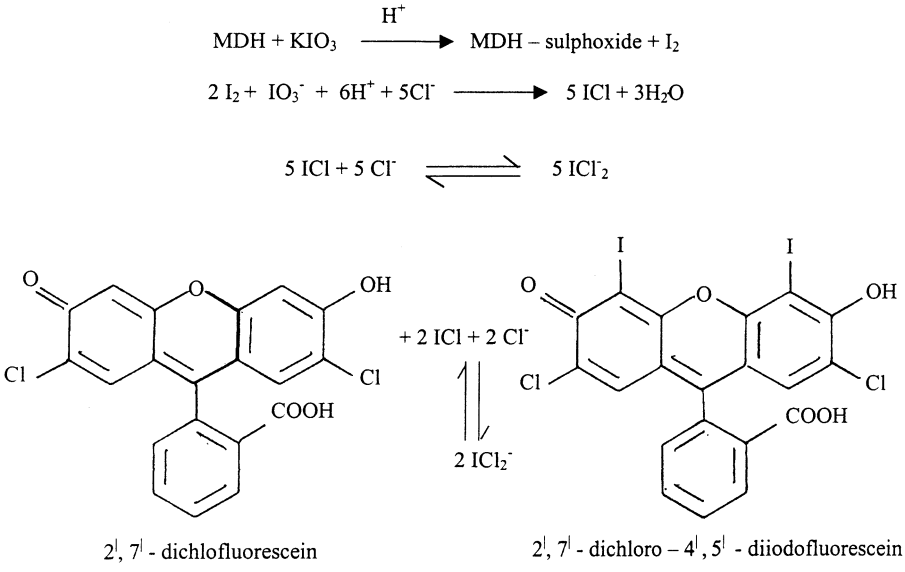

Fig. 4. Iodination reaction scheme.

dichloromethane, carbon tetrachloride was found to be the most efficient extractant giving maximum sensitivity.

3.2. Analytical parameters

Optical characteristics (for spectrophotometric methods) like Beer's law limits, detection limit, quantification limit, molar absorptivity and Sandell sensitivity are compiled in Table 1. Slope, intercept and correlation coefficient data from the linear least square treatment data are also presented in Table 1. Linear dependence of absorbance on concentration ranges given in Table 1 is evident from the regression coefficient values of 0.9892, 0.9890 and 0.9969 for methods B, C and D, respectively. As shown by the molar absorptivity values, method B is the most sensitive followed by method C, and method D the least sensitive among the three proposed methods for methdilazine.

3.2.1. Accuracy and precision, and ruggedness

The accuracy of the titrimetric procedure was determined by performing replicate determinations on a series of seven solutions each containing 10 mg of methdilazine. The high accuracy of the method is reflected by a mean recovery of 99.32% and a range of error (%) of 3.04 at 95% confidence limit. To estimate the repeatability of the procedure, a series of seven solutions each containing 10 mg of drug was run at one time. The average recovery was 9.932 mg with a range of 0.90 mg and a standard deviation of 0.3208 mg. The relative standard deviation was 3.16%.

The accuracy and precision of the spectrophotometric methods were ascertained by performing seven replicate analyses on pure drug solutions containing 60 μg (Method B), 400 μg (Method C) and 4 mg (Method D) of methdilazine in a total volume of 10 ml (B and C) and 5 ml (D). The data generated from this study are presented in Table 1 and are indicative of the fair degree of accuracy and precision.

For a better picture of reproducibility on a day-to-day basis, analyses were performed on the same amounts (used to evaluate the within-day repeatability) each day for 5 days. Analysis of variance applied to the results showed that between-day variability was, as expected, greater than within day variability. In terms of relative standard deviations, the within-day values were less than 2% and between-day values were within 3%. The latter figure probably represents the best appraisal of the precision of the procedures in daily routine use.

3.2.2. Interferences

Commonly encountered excipients such as starch, lactose, talc, gelatin, stearate, alginate and boric acid and were found not to interfere in the procedures when present in quantities normally found dosage forms. As can be seen from Table 1, the selectivity achieved with the proposed methods was good, and so these methods are useful for the determination of methdilazine in formulations.

3.2.3. Application to dosage forms

The proposed methods were applied to the determination of methdilazine in dilosyn tablets and in syrup. The results shown in Table 2 are in good agreement with the amounts claimed by the manufacturers.

Table 1
Optical characteristics, precision and accuracy of the spectrophotometric methods

Parameter	Method B	Method C	Method D
Beer's law limits (μg ml^{-1})	1.25–8.75	5.0–60.0	50–600
Detection limit (μg ml^{-1}) [b]	0.32	0.69	6.94
Quantification limit (μg ml^{-1}) [c]	1.07	2.31	23.13
Molar absorptivity (l mol^{-1} cm^{-1})	25.26×10^3	2.65×10^3	2.19×10^2
Sandell sensitivity (ng cm^{-2} per 0.001 A unit)	13.18	125.63	1520.22
Regression coefficient, *r*	0.9892	0.9890	0.9969
Regression equation [a]			
Intercept, *a*	0.5855	-9.6×10^{-3}	-3.6×10^{-3}
Slope, *b*	−0.0446	9.1×10^{-3}	6.7×10^{-4}
Range (μg)	1.01	1.40	15.82
Standard deviation (μg)	0.37	0.58	8.63
Relative standard deviation (%) ($n = 7$)	0.62	0.14	2.17
Range of error (%) [d]	0.59	0.14	2.09

[a] $A = a + bC$ where 'A' is the absorbance for concentration 'C' in μg ml^{-1}.
[b] Calculated from the formula: $D_L = 3.3s/b$ where D_L stands for detection limit. s, Standard deviation of blank and b, slope of calibration curve.
[c] Calculated from the formula: $Q_L = 10s/b$ where Q_L stands for quantification limit.
[d] At 95% confidence level.

Table 2
Results of analysis of dilosyn tablets and syrup by the proposed methods

Method	Tablets (8 mg MDH per tablet) [b]			Syrup (4 mg MDH per 5 ml) [b]		
	Found (mg) [a]	Recovery (%)	RSD (%)	Found (mg) [a]	Recovery (%)	RSD (%)
A	7.97	99.58	0.84	3.87	96.78	0.63
B	7.82	97.76	1.56	3.85	96.34	1.28
C	7.87	98.32	1.03	3.88	97.05	0.84
D	8.03	100.43	0.28	3.90	97.48	0.33

[a] Average value of five replicate analyses.
[b] Marketed by Glaxo Ltd., Mumbai.

4. Conclusions

The work clearly demonstrates that the four proposed methods are good alternatives to the already existing methods for methdilazine interms of simplicity, selectivity and sensitivity. The results obtained by using the four methods (Table 2) have statistically been evaluated with regard to accuracy and precision. The results in Table 2 show that the titrimetric (A) and extractive spectrophotometric (D) methods have similar accuracy and precision and better than methods B and C because the reaction stoichiometry (Method A) is constant with contact time upto 2 h, and iodine extracted into carbon tetrachloride (Method D) is stable for several days if protected in tightly stoppered flasks. All the methods employ reagents, which are stable enough and need no special precautions during storage or use. The present procedures, therefore, offer, in addition to satisfactory accuracy and precision, a convenient solution to a number of problems associated with the earlier methods. The proposed titrimetric method (A) is the first such procedure ever reported for MDH. The spectrophotometric method (B) describes the most sensitive assay procedures ever reported for MDH with a molar absorptivity (ε) of 2.5×10^4 l mol^{-1} cm^{-1} compared with earlier methods [5–9] with ε value averaging $\sim 10^3$ l mol^{-1} cm^{-1} or even less [8,9]. Method C, though not as sensitive as method B, uses a novel reaction; does not require heating unlike the reported methods [6–8], is more sensitive than haematoxylin [8] and ion-pair complex [9] methods; and is based on the measurement of the colour system which is stable for more than 18 h compared with less stable radical cation used in earlier methods [6,7]. Method D is less sensitive and involves extraction step but uses very stable coloured species and is not critically dependent on any experimental variable including the extraction time, which is only 2 min.

The methods, however, are without disadvantages, the most glaring being the contact time of 15–20 min before subsequent measurements are made. The other disadvantages include extraction (Method D) and heating (Method B) steps, which, however, are offset by numerous advantages over existing methods for the assay of MDH.

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