ScienceAsia 29 (2003): **37-44**

Four New Vanadometric Methords for the Assay of Methdilazine in Bulk Drug and in Pharmaceutical Formulations

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Received 15 Mar 2002
Accepted 11 Sep 2002

ABSTRACT Two titrimetric and two spectrophotometric methods, which are simple, accurate, precise and economical, are described for the determination of methdilazine hydrochloride in bulk form and in formulations. All the methods are based on the oxidation of the drug by metavanadate in acidic condition followed by measurement of unreacted oxidant or vanadium (IV) produced in the redox reaction. In one titrimetric method (A), the drug is treated with a known excess of metavanadate in sulphuric acid medium and after the redox reaction, the residual oxidant is back titrated with iron (II) ammonium sulphate using N-phenylanthranilic acid indicator. The other titrimetric method (B) is based on the titration of vanadium (IV) produced in the redox reaction with cerium (IV) sulphate using ferroin as indicator and in the presence of acetone catalyst. In one spectrophotometric method (C) the drug is treated with a known excess of metavanadate and, after the reaction is judged to be complete, the unreacted metavanadate is determined by complexing with chromotropic acid in the same sulphuric acid medium employed for the oxidation step. The other spectrophotometric method (D) relies on the determination of vanadium (IV), a product of the redox reaction, by interacting with ferriin reagent and measuring the resulting ferroin at 510 nm.The working conditions of the methods have been optimised. Optical characteristics such as Beer's Law limits, detection and quantification limits, molar absorptivity and Sandell sensitivity values have been reported for spectrophotometric methods. The methods were successfully applied to the determination of methdilazine in tablets and syrup, and the results obtained were in agreement with the label claim. Further, the validity of the procedures were confirmed by applying the standard-addition technique.

KEYWORDS: methdilazine, determination, titrimetry, spectrophotometry, ferriin reagent, chromotrophic acid, pharmaceutical formulations.

Methdilazine hydrochloride (MDH) is used as an antihistaminic drug and it is also found to possess antipruritic action.[1] Quantitation of MDH has been achieved by reversed phase and ion-exchange electrochromotography[2] and high-performance liquid chromatography (HPLC),[3] and separation by thin-layer chromotography.[4] The spectrophoto-metric 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-methylbenzo-thiazolin-2-one hydrazone (MBTH) have been used to determine micro quantities of methdilazine in pharmaceuticals.[5] However, the procedures lack selectivity. The red colored 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 *in situ* from haematoxylin and chloramine-T in phosphate buffer solution, pH 7.0, was made to react with methdilazine at 70^{0}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 mg of the drug. The same authors have suggested a routine control procedure based on the extraction of methdilazine-cobaltthioc-yanate ion-associate complex[9] into chloroform and measurement at 620 nm. However, this procedure is less sensitive, the Beer's law range being 50-500 mg ml^{-1}. Another spectrophotometric method that utilizes an uncharacterised chromogen[10] formed when methdilazine was reacted with dapsone and persulphate in alkaline medium has also been reported by the same authors. MDH is reported to react with Van Urk reagent[11] 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 the drug in tablets and syrup.

This paper describes four alternative procedures for the determination of MDH. All the procedures use

metavanadate as the oxidant and depend ultimately on the determination of either surplus metavanadate when known excess is used or vanadium (IV) produced when a large unmeasured excess of oxidant is used to bring about the oxidation of the drug. The methods are simpler and more sensitive than many reported earlier [5-11] for MDH, and can be used in laboratories of underdeveloped and developing nations which can ill afford modern expensive instrumental set ups like HPLC or GLC.

Materials and Methods

Apparatus

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

Materials and Reagents

Methdilazine hydrochloride (MDH) was obtained from Glaxo Laboratories, Mumbai, India. A stock standard solution containing 2 mg ml^{-1} of MDH was prepared in double distilled water and kept in an amber-colored bottle and stored at 4°C. Working solutions of 400 mg ml^{-1} and 100 mg ml^{-1} were prepared by appropriate dilution of the stock solution for use in spectrophotometric procedures C and D, respectively.

All chemicals used were of AR grade and double distilled water was used throughout the study. An approximately 0.05 M sodium metavanadate was prepared in water and standardised[12] using standard (0.05 M) iron (II) ammonium sulphate solution which in turn was standardised with pure potassium dichromate. Metavanadate and iron (II) ammonium sulphate solutions were diluted to 0.02 M concentration to be used in titrimetric procedure (A). Metavanadate solution was diluted stepwise to a concentration of 250 mg ml^{-1} to be used for spectrophotometric work [Method C]. Cerium (IV) sulphate solution (~ 0.05 M) was prepared by dissolving 20.2 g of the reagent in 0.5 M sulphuric acid and dilution to one litre with the same acid solution and standardised using iron (II) ammonium sulphate solution.[12] N-phenylanthranilic acid (NPA) indicator was prepared by dissolving 100 mg of the indicator in 5 ml of 0.1 M NaOH and diluting to 100 ml with water. Ferroin indicator was prepared by dissolving 1.485 g of 1,10-phenanthroline in 100 ml of 0.025 M ferrous sulphate. Ferriin reagent was prepared by dissolving 0.16 g iron (III) ammonium sulphate and 0.198 g of 1, 10-phenanthroline base in 2 ml of 1 M hydrochloric acid and diluting to 100 ml with water. 0.1% (w/v) Chromotropic acid reagent was prepared by dissolving 0.1 g of the reagent in 100 ml of water. Aqueous solutions of sulphuric acid (10 M), ammonia (1:1 and 6 N) and hydroxylammonium chloride (5%) were prepared as per usual. AR grade acetone was used in titrimetric work (Method B).

Formulations

The following commercial formulations were subjected to analysis: Dilosyn tablets (Glaxo India Ltd.) containing 8 mg MDH per tablet in addition to talc (30 mg), starch (30 mg), lactose (10 mg), sodium alginate (20 mg), magnesium stearate (20 mg), and gum acacia (20 mg) and dilosyn syrup containing 4 mg MDH per 5 ml along with 0.5 ml alcohol and flavoured sorbitol base (colour - sunset yellow). Forty tablets were accurately weighed, and ground in a mortar until homogeneous. A portion of the powder equivalent to 200 mg of MDH was weighed into a 100 ml volumetric flask, to which 60 ml of water was added and shaken thoroughly for about 20 min to extract the drug into the aqueous phase. Then, the content in the flask was diluted to the mark with water, mixed well and filtered using a quantitative filter paper. The first ten ml portion of the filtrate was discarded. An appropriate aliquot of the filtrate was used as such for analysis by titrimetric procedure, and the filtrate was suitably diluted to 100 mg ml^{-1} and 400 mg ml^{-1} solutions for spectrophotometric study. In the case of dilosyn syrup, the content of 2 bottles (115 ml per bottle) were quantitatively transferred into a separating funnel. The bottles were washed with water and the washing was also transferred into the separator. The content was rendered alkaline to litmus paper with 6 N ammonia solution and 1 ml was added in excess. The contents were then extracted with 3 x 20 ml portions of chloroform, the organic extracts were evaporated to dryness on a steam bath and the residue was dissolved in 0.1 M hydrochloric acid and made up to 100 ml with water in a volumetric flask. An aliquot of this solution containing 1.84 mg MDH per ml was used for titrimetric analysis (Methods A and B). For methods C and D, the solution was diluted to 400 and 100 mg ml^{-1}, respectively, and assayed using a convenient aliquot.

Procedures

Method A *(based on the back titration of unreacted metavanadate)*

A 10 ml aliquot solution of the standard or pharmaceutical preparations containing 1-20 mg of MDH was placed in a 100 ml titration flask and made acidic by adding 5 ml of 10 M sulphuric acid. Then, 10 ml of 0.02 M sodium vanadate solution was added by means of a pipette. The content was mixed well and kept aside for 5 min with occasional shaking to facilitate the oxidation of the drug as indicated by the disappearance of the red colour of the radical cation. Lastly, 2 drops of NPA indicator were added and unreacted vanadate was titrated with standard 0.02 M

iron (II) ammonium sulphate solution to a colourless or green end-point. A blank was run in the same way with 10 ml of water. The drug content was calculated from the equation:

$$\text{Amount (mg)} = \frac{(B\text{-}S)\, M_W M}{n}$$

where

B = volume of iron (II) solution consumed in the blank titration, ml
S = volume of iron (II) solution consumed in the sample titration, ml
M_W = molecular mass of the drug.
M = molarity of vanadate solution
n = number of moles of vanadate reacting with each mole of drug

Method B *(based on the titration of vanadium (IV))*

A 10 ml aliquot of the solution of the standard or pharmaceutical formulations equivalent to 5 – 12 mg of MDH was transferred into a 100 ml conical flask by means of a pipette. The solution was acidified with 2 ml of 10 M sulphuric acid. Then, 10 ml of 0.05 M metavanadate solution was added, and the content was mixed by swirling and set aside for 5 min for the oxidation reaction to complete. Finally, 10 ml of acetone and 2 drops of ferroin indicator were added, and the vanadium (IV) produced in the redox reaction was titrated with standard 0.02 M cerium (IV) sulphate to a faint blue colour. The amount of the drug was calculated using the equation:

$$\text{Amount (mg)} = \frac{VMM_W}{2}$$

where

V = volume of cerium (IV) solution consumed, ml
M = molarity of cerium (IV) solution
M_W = molecular mass of the drug

Method C *(based on the spectrophotometric measurement of unreacted vanadium (V))*

Into a series of 10 ml volumetric flasks, 0, 0.25, 0.5 ..... 1.75 ml of 400 mg ml^{-1} of standard MDH solution was transferred by means of a microburette. The volume was adjusted to 2.0 ml by adding adequate quantity of water. The solution was made acidic by adding 1 ml of 10 M sulphuric acid, and then, 2.5 ml of 250 mg ml^{-1} of sodium metavanadate was added to each flask and set aside for 25 min. After the oxidation reaction was judged to be complete, 0.5 ml of 0.1% chromotropic acid solution was added followed by 1 ml of 5% hydroxylammonium chloride solution to each flask. The volume was made up to the mark with water, mixed well and the absorbance was measured at 420 nm against water blank. A calibration curve was prepared or a regression equation was worked using the Beer's law data. A convenient volume of the pharmaceutical preparation solution was treated in the same manner and its concentration was read from the standard curve or calculated from the regression equation.

Method D *(based on spectrophotometric measurement of vanadium (IV))*

Different aliquots, ranging from 0.5 to 2.5 ml of 100 mg ml^{-1} standard MDH solution, were transferred into a series of 10 ml volumetric flasks and the overall volume was adjusted to 3 ml by adding requisite volume of water. Then, 0.5 ml each of 10 M sulphuric acid and 0.05 M vanadate was added to each flask, the content was mixed well and set aside for 5 min to facilitate the oxidation of the drug to complete. Then, 2 ml of each of 10 M acetic acid and ferriin reagent was added successively, and after 5 min, 2 ml of 1:1 ammonia was added to each flask and diluted to the mark with water. The solution was mixed well and the absorbance was measured at 510 nm against water blank after 10 min. A calibration curve was prepared or a regression equation was worked out. A suitable aliquot of the 100 mg ml^{-1} formulation solution was treated in the same manner and its concentration was read from the calibration graph or deduced from the regression equation.

Results and Discussion

MDH being a N-gsubstituted phenothiazine derivative undergoes two step oxidation by metavanadate in sulphuric acid medium: first to a red coloured radical cation and finally to a colourless sulphoxide.[13] In the process vanadium (V) becomes reduced to vanadium (IV). In methods A and C, the drug is treated with a known excess of the oxidant, and the unreacted oxidant is determined either by back titration (A) or by spectrophotometry (C) after complexing with chromotropic acid in the same acidic conditions. The other two methods are based on the determination of vanadium (IV) formed in the redox reaction between MDH and a large excess of oxidant, either by titrating with cerium (IV) sulphate (Method B) or by measuring the absorbance of the resulting colour from the reaction of vanadium (IV) with ferriin (Method D).

Method A

Metavanadate was found to react quantitatively with MDH in sulphuric acid medium. The reaction was found to be slow in hydrochloric or phosphoric acid medium. A 5 ml volume of 10 M H_2SO_4 in a total volume

of 25 ml was found adequate for both oxidation and back titration steps. Stoichiometric study revealed that 2 moles of metavanadate reacted with one mole of MDH, an observation which is in conformity with the reaction scheme given in Fig 1.[14] The reaction stoichiometry indicated that only the S-atom of the drug was oxidised by metavanadate and other sites of the drug molecule were unaffected. For 1-20 mg range studied, a 10 ml volume of 0.02 M metavanadate was found sufficient to cause oxidation of the drug in 5 min and the suitable amount of unreacted metavanadate was left for back titration. Larger quantities of oxidant, i.e., 10 ml of 0.03 or 0.05 M metavanadate did not affect the stoichiometry of the reaction.

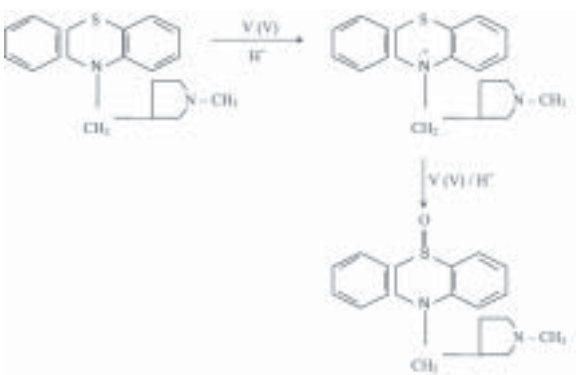

Fig 1. Oxidation scheme for MDH by metavanadate.

Method B

Of the few titrimetric procedures[15-18] available for the determination of vanadium (IV), the most convenient and simple method is the titration with cerium (IV) in acidic solution employing ferroin as an indicator and in the presence of acetone as a catalyst.[18] Method B is based on the oxidation of MDH to sulphoxide by a large excess of metavanadate in acid medium, and the titration of the resulting vanadium (IV) with cerium (IV) sulphate as described by Sriramam *et al*.[18] For the oxidation of drug as well as the titration of vanadium (IV), 0.6 - 0.8 M concentration of H_2SO_4 was found adequate. As expected, the reaction ratio was found to be 1:2 (drug : metavanadate). For the range of drug amount investigated (5-12 mg), 10 ml of 0.05 M metavanadate were found sufficient to effect oxidation of the drug in about 5 min. Contact times upto 30 min had no effect on either the stoichiometry or the results of assay.

The relation between the drug amount and the titration end-point in both methods was examined. The molar ratio of the drug and the oxidant at end-point of titration was found to be 1:2, suggesting that the reaction between MDH and vanadate proceeds stoichiometrically in the ratio 1:2. However, in method B, the titration should be performed slowly near the end-point with an interval of at least 20 s. between two additions.

Method C

In acid solution, chromotropic acid was found to give a yellow-coloured complex with metavanadate. Since metavanadate easily oxidises MDH in acidic conditions, the colour reaction between metavanadate and chromotropic acid was utilised for estimating microgram quantities of MDH.

In the present investigation, a known and excessive vanadate was used to oxidise MDH in H_2SO_4 medium to a colourless sulphoxide and the unreacted metavanadate was determined by reacting with chromotrophic acid in the same acidic condition. The same procedure was followed omitting MDH (blank).

MDH when added in increasing amounts, consumes metavanadate and consequently there is concomitant fall in metavanadate concentration. This is observed as a proportional decrease in the absorbance of the yellow colour on increasing the concentration of MDH. The decreasing absorbance values at a maximum absorption wavelength of the product were plotted against the increasing concentration of MDH to obtain a calibration graph.

By a preliminary study it was found that upto 62.5 mg ml^{-1} sodium metavanadate could be determined with chromotropic acid under the described experimental conditions. Hence different concentrations of MDH were reacted with a fixed concentration (62.5 mg ml^{-1}) oxidant in the assay procedure. In this method, two blanks were prepared. The reagent blank which contained the optimum concentrations of acid, metavanadate and chromo-tropic acid gave maximum absorbance. The other blank was prepared in the absence of oxidant and drug. The absorbance of the second blank was negligible, hence, all measurements were made against water. The developed colour was stable for several weeks, when the absorbance of the species formed following the general procedure was measured periodically.

Since the oxidation of MDH to sulphoxide by metavanadate was slow in HCl and H_3PO_4 media, H_2SO_4 was chosen as the reaction medium to effect the oxidation. A 1 ml of 10 M H_2SO_4 in a total volume of ~5 ml was found optimum with a contact time of 5 min. The same acid concentration was maintained for the determination of unreacted metavanadate with chromotropic acid, although the absorbance of the yellow chromogen was found to be unaffected in 0.1 to 2.00 M overall H_2SO_4 concentration. A 0.5 ml of 0.1% chromotropic acid and 1 ml of 5% hydroxylammonium chloride were found adequate to determine the unreacted metavanadate.

Method D

One of the sensitive spectrophotometric methods reported for vanadium (IV) involves the reduction of ferriin by vanadium (IV) to the orange-red ferroin and its measurement at 510 nm.[18] In method D, excessive vanadium (V) was used to oxidise the drug in H_2SO_4 medium to colourless sulphoxide and vanadium (IV) formed was determined by reacting it with ferriin in H_2SO_4-CH_3COOH medium and later raising the pH to facilitate the formation of ferroin.

MDH, when added in increasing concentrations, consumes vanadium (V), and consequently there will be concomitant increase in vanadium (IV) concentration. This is observed as a proportional increase in the absorbance of the coloured species with increasing concentration of MDH. The increasing absorbance values at 510 nm were plotted against the concentration of MDH to obtain the calibration graph.

$$Fe\,(Phen)_3^{3+} + V\,(IV) \rightleftharpoons Fe\,(Phen)_3^{2+} + V\,(V)$$

Since the reaction, is favoured in the presence of H_2SO_4 and CH_3COOH, 0.5 ml of 10 M H_2SO_4 and 2 ml of 10 M CH_3COOH were used to force the reaction to go to completion. Since the experimental conditions for the determination of vanadium (IV) are well established,[19] the conditions for the oxidation of MDH by metavanadate were optimised. The oxidation was slow in HCl or H_3PO_4 medium and hence, H_2SO_4 was used as the reaction medium. An overall volume of 0.5 ml of 10 M H_2SO_4 in a total volume of 4 ml was found optimum to cause oxidation of MDH in a reasonable time of 5 min.

Since ferroin is formed in the pH range of 2-9, the pH of the acidic solution was raised by adding 2 ml of 1:1 ammonia which was found adequate. Large volumes of ammonia are undesirable since iron (III) gets precipitated at high pH values.

Optical Characteristics of Spectrophotometric Methods

Optical characteristics such as Beer's law limits, detection limit, quantification limit, molar absorptivity and Sandell sensitivity are compiled in Table 1. Slope, intercept and correlation coefficient data obtained from the linear least squares treatment of the Beer's law data are also presented in Table 1. Linear dependance of absorbance on concentration ranges given in Table 1 is evident from the regression coefficient values of – 0.9929 and 0.9982, for methods C and D, respectively. As shown by the molar absorptivity value, method D is more sensitive than method C.

TABLE 1. Optical Characteristics of the Spectrophotometric Methods.

Characteristic	Method C	Method D
Reaction time, min.	25	5
Stability of the coloured species	Several weeks	> 6 months
Beer's law limits, μg ml^{-1}	0-70	5-25
Limit of detection, μg ml^{-1}	1.17	0.28
Limit of quantification, μg ml^{-1}	3.92	0.95
Molar absorptivity, l mol cm^{-1}	2.95×10^3	5.31×10^3
Sandell sensitivity, μg cm^{-2}	0.11	0.06
Regression equation *		
Intercept, a	0.45	0.04
Slope, b	-0.005	0.012
Confidence interval of intercept, α	0.45 ± 0.04	0.04 ± 0.02
Confidence interval of slope, β	-0.005 ± 0.001	0.012± 0.001
Correlation coefficient, r	-0.9929	0.9982

* Y = a+bX where Y is the absorbance for concentration X in μg ml^{-1}

Accuracy, Precision and Rugged-ness of the Proposed Methods

The accuracy of the methods was determined by analysing a known amount of MDH (within the working limits) at three levels by the proposed methods. To examine the precision of the procedures, seven replicate determinations were made on the same solution containing MDH at three levels. The range, percent error, standard deviation, relative standard deviation and range of error are presented in Tables 2 and 3, and reveal the high accuracy and precision of the proposed methods. Percent error and RSD values for lower levels in methods A, B and C, are above the accepted values and are attributed to personal errors.

For a better picture of precision on a day-to-day basis, analyses were performed on the same amount (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 1.5% and between day values were less than 2%. The latter figure probably represents the best appraisal of the precision in daily routine use.

Application to Dosage Forms

The proposed methods were applied to the determination of MDH in dilosyn tablets and syrup. The results are presented in Table 4, and indicate the high accuracy and precision of the procedures. The results were compared with those obtained by a reported procedure.[5] The application of a paired t-test

TABLE 2 . Accuracy and precision of titrimetric methods.

Method A						
Amount taken, mg	**Amount found, mg**	**Range, mg %**	**Error*, mg**	**SD, mg %**	**RSD, %**	**Range of error, Ψ %**
5.00	4.77	0.33	4.60	0.12	2.59	2.49
10.0	9.79	0.33	2.10	0.14	1.51	1.45
15.0	15.11	0.50	0.73	0.22	1.48	1.42

Method B						
Amount taken, mg	**Amount found, mg**	**Range, mg %**	**Error*, mg**	**SD, mg %**	**RSD, %**	**Range of error, Ψ %**
6.00	5.89	0.50	1.83	0.23	3.96	3.81
9.00	9.12	0.34	1.33	0.15	1.67	1.60
12.00	12.17	0.33	1.41	0.14	1.21	1.17

***** Mean value of seven determinations
Ψ at 95% confidence level

TABLE 3. Accuracy and precision of spectrophotometric methods.

Method C						
Drug taken, μm ml^{-1}	**Drug found, μm ml^{-1}**	**Range, μm ml^{-1}**	**Error*, %**	**SD, μm ml^{-1}**	**RSD, %**	**Range of error, Ψ %**
20.0	19.05	2.53	4.75	0.93	4.88	4.70
40.0	40.77	0.90	1.92	0.44	1.09	1.05
60.0	60.14	0.61	0.23	0.25	0.41	0.40

Method D						
Drug taken, μm ml^{-1}	**Drug found, μm ml^{-1}**	**Range, μm ml^{-1}**	**Error*, %**	**SD, μm ml^{-1}**	**RSD, %**	**Range of error, Ψ %**
10.0	10.15	0.38	1.50	0.17	1.69	1.63
15.0	15.37	0.37	2.46	0.17	1.12	1.07
20.0	20.44	0.56	2.20	0.23	1.13	1.09

***** Mean value of seven determinations
Ψ at 95% confidence level

and F-test (at 95% confidence level) did not show significant differences.

Recovery Experiment

To evaluate the validity and accuracy of the methods, recovery experiments were performed by adding known amounts of pure drug to the pre-analysed formulations of the drug, and reanalysing the mixture by the proposed methods. The results given in Table 5 reveal that commonly encountered excipients such as starch, lactose, talc, stearate, alginate, boric acid, etc. did not interfere when present in quantities normally found in dosage forms.

Conclusion

The proposed methods are simpler and less time consuming than many methods proposed earlier. For two procedures (B and D), the concentration of

TABLE 4. Results of analysis of dilosyn tablets and dilosyn syrup by the proposed methods.

Method	Tablets (8 mg MDH per tablet)				Syrup (4 mg MDH per 5 ml)			
	Found, mg	% recovery ± SD (n=5)	t-value (2.77)*	F-value (6.39)*	Found, mg	% recovery ± SD (n=5)	t-value (2.77)*	F-value (6.39)*
A	8.11	101.41 ± 0.23	0.32	6.35	3.92	101.58 ± 0.29	0.37	5.02
B	8.13	101.60 ± 0.27	0.35	4.61	3.97	99.73 ± 0.33	1.79	3.88
C	8.10	101.25 ± 0.24	0.89	5.84	4.04	101.13 ± 1.03	0.68	2.51
D	7.98	99.75 ± 0.31	1.85	3.50	4.02	100.73 ± 0.46	2.16	2.00
Reference	8.12	101.50 ± 0.58			4.06	101.50 ± 0.65		

***** Values in the paranthesis are the tabulated values at the 95% confidence level

TABLE 5. Recovery study by the standard - addition method.

Method	Tablets (8 mg MDH per tablet)				Syrup (4 mg MDH per 5 ml)			
	MDH in the formulation solution, mg or µg*	Pure MDH added, mg or µg*	Total found mg or µg*	Recovery of pure MDH added, % #	MDH in the formulation solution, mg or µg*	Pure MDH added mg or µg*	Total found mg or µg*	Recovery of pure MDH added, % #
A	5.07	5.00	9.86	95.80	3.05	5.00	7.79	94.80
	5.07	10.00	14.88	98.10	3.05	7.00	10.14	101.29
	5.07	15.00	19.96	99.27	3.05	10.00	12.83	97.80
B	10.16	7.00	17.21	100.71	5.98	6.00	11.85	97.83
	10.16	10.00	20.40	102.40	5.98	8.00	14.07	101.13
	10.16	12.0	22.25	100.75	5.98	14.00	19.88	99.29
C	202.50	200.00	404.72	101.11	101.13	100.00	205.74	104.61
	202.50	500.00	704.19	100.34	101.13	200.00	302.50	100.69
	202.50	700.00	901.90	99.91	101.13	300.00	405.80	101.56
D	149.63	50.00	198.92	98.58	203.00	100.00	303.03	101.03
	149.63	100.00	256.42	106.79	203.00	150.00	352.34	99.56
	149.63	150.00	302.97	102.23	203.00	200.00	397.48	97.24

***** mg in titrimetry (A and B)
µg in spectrophotometry (C and D)
Mean value of 3 determinations

vanadate need not be accurately known, there by increasing their reliability. The methods are thus suitable for the determination of MDH in formulations without interference from common tablet excipients and syrup additives, and also from the oxidation product of MDH, its sulphoxide.

Acknowledgements

The authors express their gratitude to Quality Control Manager, Glaxo India Ltd., Mumbai for a gift sample of MDH.

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