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RESEARCH ARTICLE

Determination of Mianserine using Fe^{3+}-phenanthroline by visible Spectrophotometry

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ABSTRACT:
Mianserin is used as an antidepressant medication. A visible spectrophotometric method was developed for determination of Mianserine present in bulk and tablet formulation. The basis of the proposed method is formation of a chromophore (of λ_{max} 484 nm) in presence of Fe^{3+}-Phenanthroline. Optimization of reaction conditions was carried out to get highly sensitive and stable colored complex. The proposed method does not require a pre-treatment process. The method has the advantage of simple, reproducible, selective and sensitive. Regression analysis ($r > 0.999$) shows that the plotted calibration curve exhibits good linearity in the studied range of concentration (1 – 6 µg mL^{-1}). The % recovery values falls in 98.00 – 99.66 range. As per the existing guidelines of ICH, various parameters of the method were tested for validation. %RSD results of both precision studies were observed in the range 0.181 – 0.530 and -0.135 – 0.408 respectively, indicating the satisfactory precision of the method. Low values of R.S.D. (< 2 %) were observed indicating that the proposed method is reproducible, accurate and precise. The proposed method can be used in routine analysis of Mianserine (bulk drug and pharmaceutical dosage forms) in quality control laboratories, as an alternative to the methods which require expensive instruments.

KEYWORDS: Mianserine, Phenanthroline, Oxidation-reduction, Method development, Validation.

INTRODUCTION:
Mianserin salt form (M-HCl with molecular formula $C_{18}H_{20}N_2HCl$) is one of the well-known drug used as an antidepressant. It is tetracyclic and its chemical name is 1, 2, 3, 4, 10, 14b- Hexahydro- 2- methyldibenzo [c, f] -pyrazino [1, 2- a]azepine hydrochloride (**Fig. 1**). Brain nerve cells are influenced by this drug [1-2]. Spectrophotometric [3-6], HPLC [7-10], capillary electrophoresis [11-14] and gas chromatographic methods [15-16] were used for quantitative determination of Mianserin in their formulation forms. Taking into consideration of high cost of the instruments used by researchers in these methods, phenanthroline is proposed as a chromogen in the present study.

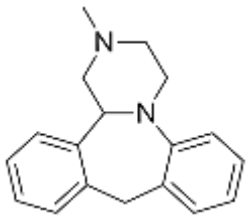

Fig. 1: Chemical Structure of Mianserine

MATERIALS AND METHODS:
TECHOMP (UV 2310) double beam UV-Visible Spectrophotometer with HITACHI software version 2.0 was used to measure the absorbance. Quartz cuvetts (10 mm path length) were used for the analysis. Digital pH meter (Elico LI-120) and balance (Shimadzu AUX-220) were used to weigh the samples and to measure pH respectively. Spectroscopic measurements were conducted at room temperature (25 ± 5 ^{0}C). All chemicals used in the present study were AR grade. In the entire process, used water was double distilled.

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Preparation of reagents:

O-phenanthroline:

Weigh accurately 200 mg of O-phenanthroline and was dissolved in 100 ml of distilled water with warming.

Fe (III) solution:

Accurately 100mg of anhydrous ferric chloride was weighed and was taken in a100 ml graduated volumetric flask. It was dissolved in little amount of distilled water and the final volume was made up to the mark with distill water.

RESULTS AND DISCUSSIONS:

Absorption Spectrum of Coloured Complex:

A characteristic absorption maximum was observed at 484 nm for the developed chormophore in determination of Mianserine by visible spectrophotometry (Fig. 2).

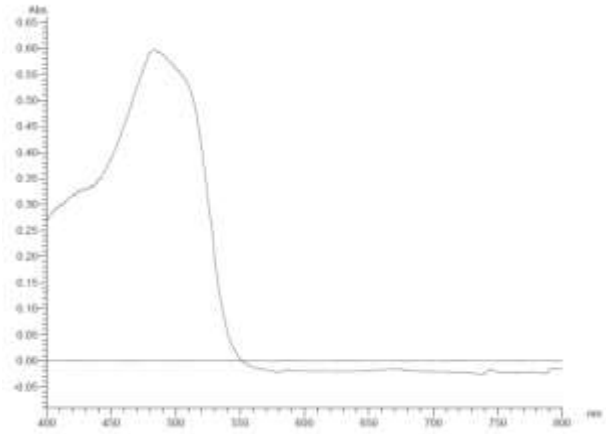

Fig. 2. Visible spectrum of Mianserine

Chromophore Formation and Chemistry:

Mianserine when treated with an oxidant [Fe(III)], it undergoes oxidation, giving products of oxidation (inclusive of reduced form of oxidant, Fe (II) from Fe (III), besides un reacted oxidant). The reduced form of Fe III (i.e., Fe II) has a tendency to give colored complex on treatment with o-PHEN (**Fig. 3**).

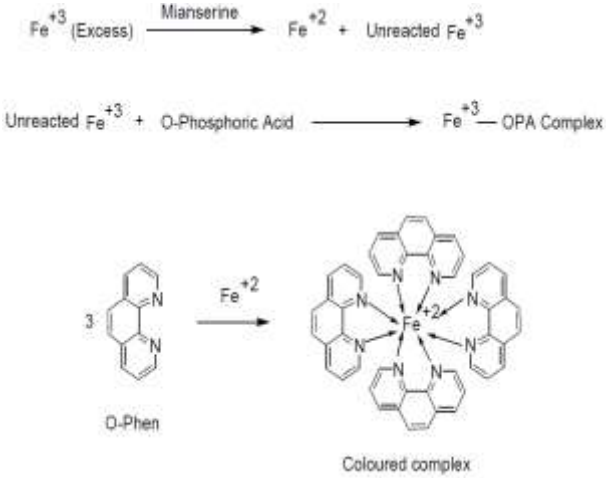

Fig. 3. Reaction of Mianserine with Fe(III)/O-PHEN

Optimized Method Procedure:

From the standard stock solution, aliquots of standard drug solution (0.5 to 3.0 ml; 20 µg/ml) was pipetted out in to a 10 ml volumetric flasks, 1.0 ml $FeCl_3$ solution and 2 ml of 1,10 Phenanthroline were added. The tube was heated in water bath up to 30 min and make up to 10 ml with distilled water. Made up to 10 ml volume and measured absorbance against the reagent blank.

Validation of Method:

Linearity and range:

The calibration curve was constructed by plotting a graph between absorbance versus concentrations and was found to be linear (Fig. 4). Three independent measurements of absorbance were carried out for each concentration (1 – 6 µg mL^{-1}) and mean value represents the point present on the calibration curve (Table 1). y = 0.1472x + 0.0012 was the linear regression equation. The correlation coefficient was greater than 0.999 and hence, the linearity of the proposed analytical method was tested. Table 2 represents different optical and regression parameters.

TABLE 1. CALIBRATION CURVE VALUES

Concentration (µg mL^{-1})	Absorbance*
1	0.154
2	0.289
3	0.441
4	0.598
5	0.726
6	0.891
* Average of three independent determinations	

Table 2. Key Parameters of Method Development and Validation

S. No.	Parameter	Observation
Optical characteristics		
1.	Apparent molar absorptivity (l mol^{-1} cm^{-1})	3.92×10^4
2.	Sandell's sensitivity (µg $cm^{-2}A^{-1}$)	0.00675
Regression analysis		
1.	Slope	0.417
2.	Intercept	0.001
3.	Regression coefficient (*r*)	0.999
Validation parameters		
1.	λ_{max}	484 nm
2.	Beer's Law Limit (Linearity, µg mL^{-1})	1-6
3.	Limit of detection (µg mL^{-1})	0.06
4.	Limit of quantitation (µg mL^{-1})	0.2
5	Stability period	12 hours

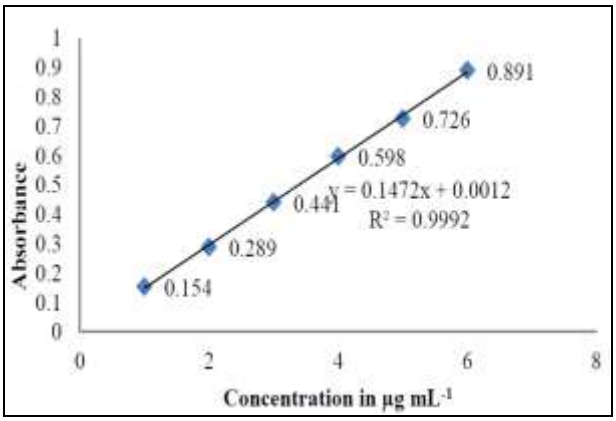

Fig. 4. Calibration graph of Mianserine

TABLE 3. RECOVERY OF MIANSERINE

Level of recovery (%)	Nominal concentration used (µg mL^{-1}) (a)	Amount of drug added (µgmL^{3}) (b)	Total amount of drug (a + b) (µg mL^{-1}) (Theoretical)	Amount of drug recovered (µg mL^{-1}) (Practical)	Statistical evaluation	% Recovery = Practical / Theoretical x 100
50	2	1	3	2.99	Mean:2.96	99.66
	2	1	3	2.97	SD: 0.020	99.00
	2	1	3	2.94	%RSD:0.692	98.00
100	2	2	4	3.97	Mean:3.95	99.25
	2	2	4	3.96	SD: 0.012	99.00
	2	2	4	3.94	%RSD:0.315	98.50
150	2	3	5	4.95	Mean:4.97	99.00
	2	3	5	4.97	SD: 0.016	99.40
	2	3	5	4.99	%RSD:0.328	99.80

Accuracy:

Percent recovery values were determined to know current method accuracy. This was accomplished by the addition of various quantities (50% to 150%) of Mianserine bulk sample to fixed quantify (10 µg mL^{-1}) in order to maintain the total amount of drug (theoretical) concentration within the linearity range. Table 3 shows that the % recovery values falls in 98.00 – 99.66 range (Table 3). Current method can be considered to be of highly accurate due to small values of %RSD as well as S.D.

Precision:

Inter-day and intraday precision were studied by selecting different three concentrations of Mianserine in the above selected range for linearity (1 – 6 µg mL^{-1}). Analysis of each concentration (of six independent series) was carryout out on consecutive days (six in numbers) as well as on the same day (Table 4). %RSD results of both precision studies were observed in the range 0.181 - 0.530 and -0.135 – 0.408 respectively, indicating the satisfactory precision of the method.

Table 4. Intraday and inter-day precision readings of the proposed method

Concentration of Meanserine (µg mL^{-1})	Concentration*			
	Intraday (Mean ± SD) (µg mL^{-1})	% RSD	Inter-day (Mean ± SD) (µg mL^{-1})	% RSD
1	1.024±0.005	0.530	1.004±0.001	0.135
3	3.008±0.005	0.181	2.995±0.012	0.408
6	6.044±0.019	0.315	6.058±0.019	0.314

***** Average of six determinations

Ruggedness:

Assay of different amounts of Mianserine (1, 3 and 6 µg mL^{-1}) was carried out by two different analysts on different days under the above given method optimized conditions in order to appraise the ruggedness of the current developed method. Lack of significant difference in the values produced by different analysts indicates the evidence for reproducible results (Table 5). Hence, ruggedness of this method is confirmed.

Table 5. Ruggedness data of Mianserine by two analysts at different days

Test Concentration of Meanserine (µg mL^{-1})	Concentration*	
	Analyst change	
	Mean ± SD (µg mL^{-1})	% RSD
1	0.997±0.005	0.545
3	2.988±0.005	0.182
6	6.044±0.019	0.315

***** Average of six determinations

Limits of detection and quantification:

As per the ICH guidelines (2005), LOD and LOQ were calculated to determine the sensitivity of the proposed method using formula (3.3 × σ /S) and (10 × σ /S) respectively taking into consideration of ratio between signal and noise [17-18], where S (calibration curve slope) and σ (S.D. of the response). The corresponding calculated values for Mianserine determination are given below.

LOD = 0.06 µg mL^{-1} and
LOQ = 0.29 µg mL^{-1}

Analysis of Pharmaceutical Formulations:

Considering the average weight as basis, the amount of API present in formulation (Tablet) was determined by measuring the absorbance values of chromophores derived from the extracts of Mianserine tablets (Deipnon®) (Table 6). To determine the amount of Deipnon present in the tablet formulations, the above suggested method can be used because the recovery values of the API is good. It indicates the non-

interference to the above method from common excipients. In developing countries, the most opted analytical technique is spectrophotometry to carry out the routine analysis in QC laboratories of industries [19-21]. Hence, the above method which comprises Mianserine as a complexing agent can be applied to determine the quantity of Deipnon present in pure and tablet formulations.

TABLE 6. ESTIMATION OF MIANSERINE FROM ITS FORMULATION BY VISIBLE SPECTROPHOTOMETRIC METHOD

Formulation	Labeled amount (mg)	Amount found* (mg)	% Drug Recovered	%RSD
Deipnon	30mg	2.950±0.020	98.33	0.678

* Average of three determinations

CONCLUSIONS:

The proposed method is simple and straightforward as there is no need to main complicated conditions (like intricate sample treatment, tiresome liquid-liquid extractions of chromophores, vigilance to maintain critical optimum pH etc) and can be performed without usage of expensive or sophisticated instrumentation. All these advantages help to encourage the proposed method in routine analysis of Mianserine (bulk drug and pharmaceutical dosage forms) in quality control laboratories, as alternatives to the HPLC and LCMS/MS methods.

List of symbols and Abbreviations:

S: Calibration curve slope
σ: Standard deviation of the response
R.S.D.: Relative Standard Deviation
HPLC: High Performance Liquid Chromatography
GC: Gas Chromatography
PHEN: O-phenanthroline
LOD: Limit of quantification
LOQ: Limit of quantification

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