



Research Article

ISSN : 2277-3657  
CODEN(USA) : IJPRPM

## Spectrophotometric estimation of nisoldipine in tablet dosage form

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### ABSTRACT

Two sensitive and inexpensive spectrophotometric methods for quantitative analysis of nisoldipine in tablets have been developed by utilizing the redox properties of 1,4-dihydropyridine pharmacophore. Nisoldipine on reduction with Zn/HCl followed by coupling with N-methyl-1,4-benzoquinoneimine yield a chromophore which absorb at  $\lambda_{max}$  of 520 nm (Method A). Method B uses the oxidation potential of nisoldipine followed by coupling reaction with 3-methyl-2-benzothiazolinone hydrazone in the presence of ferric chloride to give purple colored chromogen which absorbs at  $\lambda_{max}$  of 623 nm. Beer's law was obeyed over the concentration range of 5.0–30.0 and 40–240  $\mu\text{g/ml}$  with methods A and B, respectively. The proposed methods were found to be specific, precise, linear, accurate and sensitive. The methods can be effectively applied for the estimation of nisoldipine in tablets with recoveries of 99.30% and 99.24% with method A and method B respectively.

**Keywords:** Validation, Nisoldipine, Spectrophotometric, Metol (4-(methylamino) phenol), MBTH (-Methyl-2-benzothiazolinone hydrazone).

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### INTRODUCTION

Nisoldipine, a 1,4-dihydropyridine derivative marketed as Sular<sup>®</sup>, is an FDA approved controlled-release formulation for the treatment of hypertension. It antagonizes calcium channels thereby inhibiting the influx of calcium into smooth and cardiac muscles resulting in dilatation of arteries. The potency of antagonistic effect is more on vascular smooth muscles than cardiac muscles [1].

Chemically Nisoldipine is, 3,5-pyridinedicarboxylic acid-1,4-dihydro-2,6-dimethyl-4-(nitrophenyl)-methyl-2-methylpropyl ester. The structure is given in figure- 1.

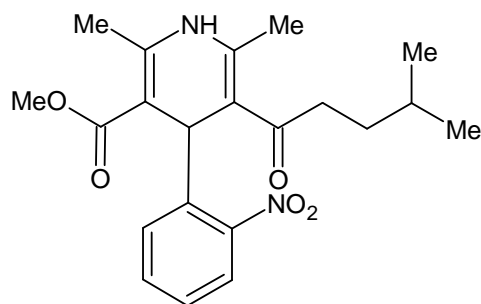


Figure- 1

Few methods, such as differential pulse voltammetry, polarography and HPTLC [2-4] have been used for estimation of nisoldipine in pharmaceuticals. Some techniques revealed the analysis of nisoldipine along with its related substances and degradation products [5] utilizing the methods of liquid chromatography and mass spectrometry. Bio-analytical methods using hyphenated techniques have also been reported [6-8]. Some methods of analysis utilizing the concepts of UV [9], HPLC [10-11] and visible spectroscopy [12-13] for determination of nisoldipine have also been reported. Most of the methods mentioned above have a lot of drawbacks such as matrix interferences, use of costly reagents and chemicals and long running time. Earlier, I have also reported the determination of nisoldipine by ion-pair complex formation [14]. In continuation, this study was undertaken to develop another easy and simple method for analysis of nisoldipine which can be used with sufficient degree of accuracy and precision.

## MATERIALS AND METHODS

### 2.1 Apparatus

Shimadzu UV/Vis double beam spectrophotometer (model 1800) and Jenway UV/Vis double beam spectrophotometer (model 6800) with 1 cm matched quartz cells was used for all spectral measurements. All chemicals used were of A.R. grade from Sigma-Aldrich. The pure drug was taken from Exela Pharmsci. Pvt. Ltd and Sular<sup>®</sup> tablets were procured from the USA.

### 2.2 Reagents

Methanol

Double distilled water

MBTH (0.2% w/v in water)

Ferric chloride (0.5 % w/v in water)

Hydrochloric acid (1 and 4 M)

Metol (0.2 % in water)

Buffer solutions (pH 2.9)

Potassium dichromate (0.01 M)

### 2.3 Preparation of standard and sample solutions:

In a suitable volumetric flask, nisoldipine (100 mg) was dissolved in methyl alcohol (30 ml). To the resulting methanolic solution, 4N hydrochloric acid (10 ml) and zinc dust (1.1 g) were added and stirred vigorously for about 5 minutes. After 1 h the reaction mixture was filtered through 0.45 $\mu$  filter press. The residue was rinsed with methyl alcohol thrice (3 x 10 ml) and final volume made up to 100 ml with methyl alcohol. Finally, the standard concentration of 1mg/ml of reduced nisoldipine was prepared with methyl alcohol. Sample solution was prepared by weighing ten tablets and taking 100 mg of its equivalent powder for the study using the above-mentioned procedure.

#### 2.3.1 Method – A

To aliquots of reduced nisoldipine solutions ranging from 0.5-0.3 ml (1 ml = 100  $\mu$ g), buffer (pH 2.9; 1.5 ml), 4-(methylamino) phenol (0.2%; 1.5 ml) and potassium chromate (0.01 M; 1.2 ml) solutions were added. The resulting solutions were diluted to 10 ml with bi-distilled water and allowed to stand for 18 min. The absorbance of resulting solutions was determined at 520 nm against blank and percentage of drug calculated from Beer-Lambert's plot. The sample was stable for more than 2h.

### 2.3.2 Method - B

To aliquots of reduced nisoldipine solutions ranging from 0.4-2.4 ml (1 ml = 1000 µg), ferric chloride (0.5% in water; 1 ml) and MBTH (0.2% w/v in water; 1 ml) solutions were added. The resulting solutions were diluted to 10 ml with bi-distilled water and allowed to stand for 10 min. The absorbance of resulting solutions was determined at 623 nm against blank and percentage of drug calculated from Beer–Lambert's plot. The sample was stable for more than 2h.

## RESULTS AND DISCUSSION

Table 1 represents the common attributes of method A and method B associated with UV/Vis spectrophotometry. The regression study was performed by methods of least square for calculations of slope (b), intercept (a) and correlation (r). The average of eight measurements was taken for calculations of % relative standard deviation and range of error. The data demonstrated sufficient degree of precision for both methods. The results obtained with the proposed methods (method A and B) are comparable with that of other UV methods reported in the literature.

### 3.1 Optimization of Variables

Both the spectrophotometric methods were optimized for different parameters such as diluents, wavelength selection, water and organic solvent ratio etc. It was done by keeping one variable fixed and changing the other, one at a time. Beers-Lambert law was followed suitably for the parameters and ranges selected for both methods. No interferences of any kind were observed during the study from excipients or diluents.

### 3.2 Validation

#### 3.2.1 Linearity

The linearity of the proposed methods was determined by analyzing different concentrations of standard solutions of nisoldipine. Different parameters of linearity are presented in table 1.

#### 3.2.2 Accuracy

Recovery studies were performed by method prescribed as per ICH quality guidelines by adding 16, 20 and 24 mg of standard nisoldipine (80%-120%) in triplicate. The percentage recovery of  $99.3233 \pm 0.7026$  with method A and  $99.4322 \pm 0.7026$  with method B indicates the suitability of proposed methods. (Acceptance criteria = 98%-102%). (Table 2)

#### 3.2.3 Precision

Intra-day precision studies were demonstrated for six sample solutions of nisoldipine analyzed two times in a day. The assay content and RSD shown in table 3 and 4 indicate that both proposed methods were precise within the specified ranges. (Acceptance criteria for  $RSD \leq 2\%$ ). (Table 3 and 4)

#### 3.2.4 Robustness

Two different instruments were used to study the robustness of the proposed methods. The relative standard deviation values of 0.5398 and 0.5134 for method A and method B respectively indicate the suitability of the method.

#### 3.2.5 Limit of Detection (LOD) and Limit of Quantitation (LOQ)

The LOD and LOQ of the proposed methods were determined by repeating the measurements ten times at 520 and 623 nm. The values were found to be 5-30 µg/ml and 40-240 µg/ml for method A and method B respectively (Table 1).

#### 3.2.6 Specificity:

For estimating the specificity, nisoldipine nitrosophenyl pyridine, a degradation product of nisoldipine was used in varying amount and interference was determined. The interference was found to be minimal with reagents, diluents and common excipients.

## DISCUSSION

The structure of nisoldipine (1) contains one aromatic nitro functionality which on treatment with zinc and hydrochloric acid is reduced to an amino group (2) (Scheme 1).

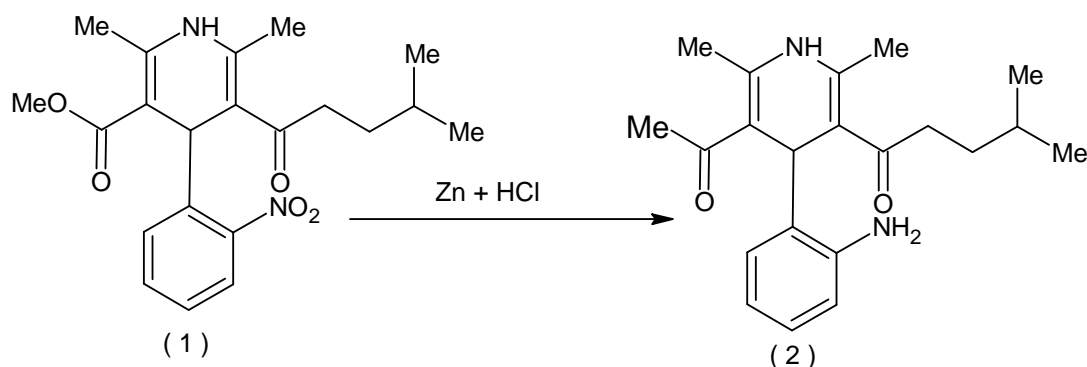


Figure 2: Scheme 1

### 3.3.1 Method A

In method A, reduced nisoldipine (2) was coupled with N-methyl-1,4-benzoquinoneimine (4) to form a purple colored chromophore (5), with  $\lambda_{\text{max}}$  of 520nm (Scheme-2). N-methyl-1,4-benzoquinoneimine (4) was formed by the oxidation of 4-(methylamino)phenol (Metol) (3) with potassium dichromate.

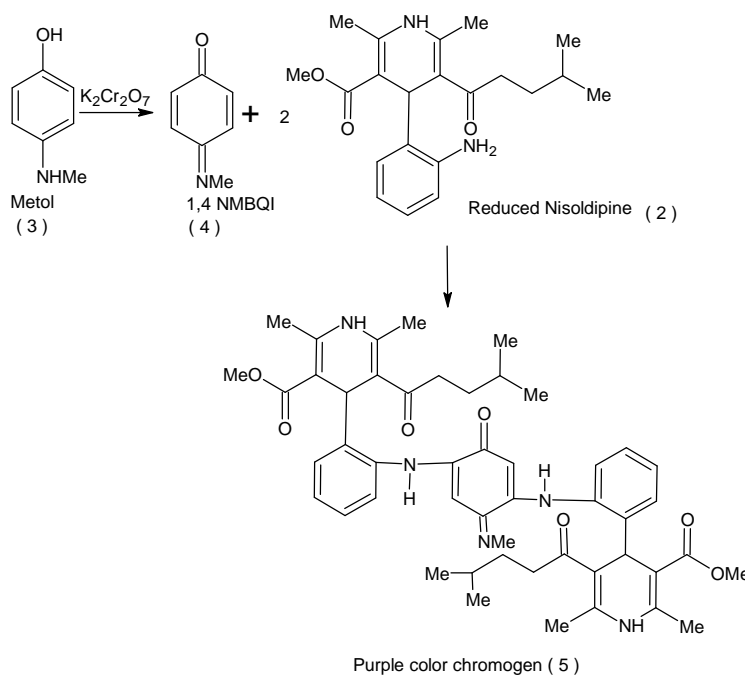


Figure 3: Scheme 2

### 3.3.2 Method- B

Various coupling reagents are employed to develop a suitable chromophore to absorb visible light. 3-Methyl-2-benzothiazolinone hydrazone (MBTH) (6), named Besthorn reagent was synthesized in 1910. It is mainly used to prepare azo dyes and employed in the analysis of various organic compounds by an oxidative coupling reaction.

MBTH is a well-known reagent used to couple oxidatively [15] various functionalities such as phenols, aromatic amines, heterocyclic bases and compounds containing active methylene group to form highly colored product depending upon the reaction conditions.

In acidic media [16-21] ferric chloride form, a resonance stabilized intermediate, an active coupling species upon the oxidation of MBTH. The intermediate of MBTH further undergoes electrophilic substitution [22-23] with the reduced nisoldipine moiety to form a colored product showing an absorption peak at 623 nm (Scheme 3).

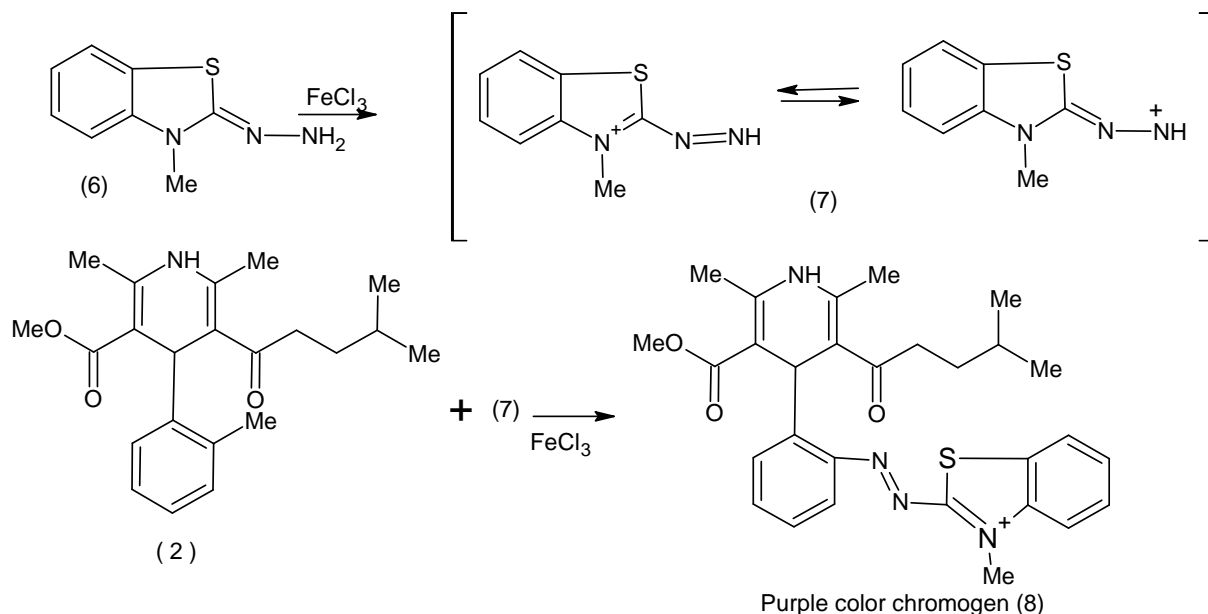


Table 1: Optical Characteristics and Linearity Parameters

Optical Characteristics	METOL (Method A)	MBTH (Method B)
$\lambda_{max}$	520	623
Beer's law limits (mg/ml)	5-30	40-240
Molar absorptivity (L/mol.cm)	$1.389 \times 10^3$	$1.348 \times 10^3$
Sandell's sensitivity ( $\text{mg cm}^{-2} - 0.001$ absorbance unit)	0.0304	0.2816
Regression equation (Y*)		
Slope (b)	0.036	0.034
Intercept (a)	0.0093	0.0018
Coefficient of correlation	0.9998	0.9997
Percentage RSD (Range of errors**)		
Confidence limits (0.05 level)	0.00228	0.00233
Confidence limits (0.01 level)	0.00338	0.0031
*Y= bC + a where C is the concentration of nisoldipine in mg/ml and Y is the absorbance at the respective $\lambda_{max}$		
** For six measurements.		

Table 2: Accuracy Studies (% Recovery)

	Labeled Amount ( $\mu\text{g}$ )	Amount Added ( $\mu\text{g}$ )	% Recovery	RSD
Method A	20	16	$99.4231 \pm 0.7025$	0.4074
	20	20	$99.1244 \pm 0.7017$	0.4102
	20	24	$99.3543 \pm 0.7026$	0.3628
Method B	20	16	$99.3231 \pm 0.7026$	0.3052
	20	20	$99.2241 \pm 0.7027$	0.4136
	20	24	$99.1641 \pm 0.7019$	0.4151

Table 3: Precision Studies (Intra-day precision)

	Concentration ( $\mu\text{g/ml}$ )	% Drug Content	Mean RSD
Method A	10	$99.958 \pm 0.7874$	0.48225
	20	$99.928 \pm 0.1014$	
	30	$99.297 \pm 1.114$	
Method B	10	$99.3231 \pm 0.7026$	0.4662
	20	$99.2241 \pm 0.7027$	
	30	$99.1641 \pm 0.7019$	

Average of three determinations (n=3)

Table 4: Precision Studies (Intra-day precision)

		Concentration (µg/ml)	% Drug Content	Mean RSD
Method A	Analyst 1	20	99.69	0.5297
Method B	Analyst 2	20	99.79	0.5213

### CONCLUSION

The proposed spectrophotometric methods are suitable for determination of nisoldipine and utilize inexpensive reagents during analysis. Both methods are validated as per the latest ICH guidelines. The results obtained confirmed the methods to be simple, sensitive, accurate, precise, and economical and can be used in the determination of nisoldipine in pharmaceutical dosage forms in a routine manner.

### Acknowledgement

The author is thankful to the President, Jazan University for providing the necessary facilities and Exela Pharmsci. Pvt. Ltd. for providing the free gift sample of nisoldipine for the study.

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