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Research Article

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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 λ_{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 λ_{max} of 623 nm. Beer's law was obeyed over the concentration range of 5.0–30.0 and 40-240 µg/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).

INTRODUCTION

Nisoldipine, a 1,4-dihydropyridine derivative marketed as Sular®, 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.

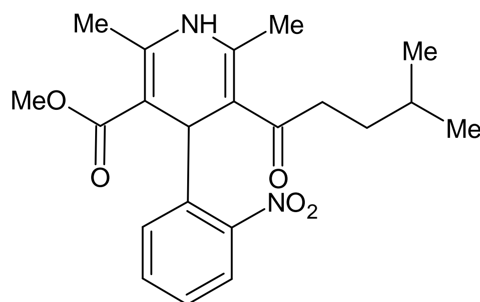

Figure- 1

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 bye 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® 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 0.45µ 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 µg), 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 ± 0.7026 with method A and 99.4322 ± 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 ≤ 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).

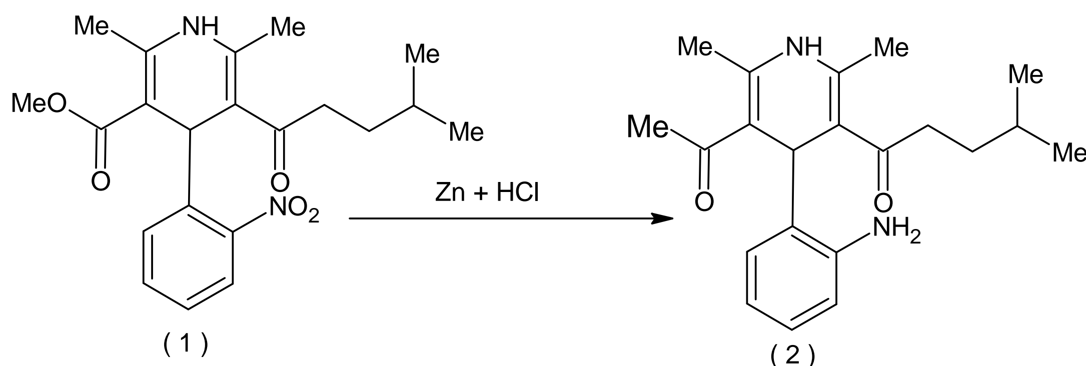

Figure 2: Scheme 1

3.3.1 Method A

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

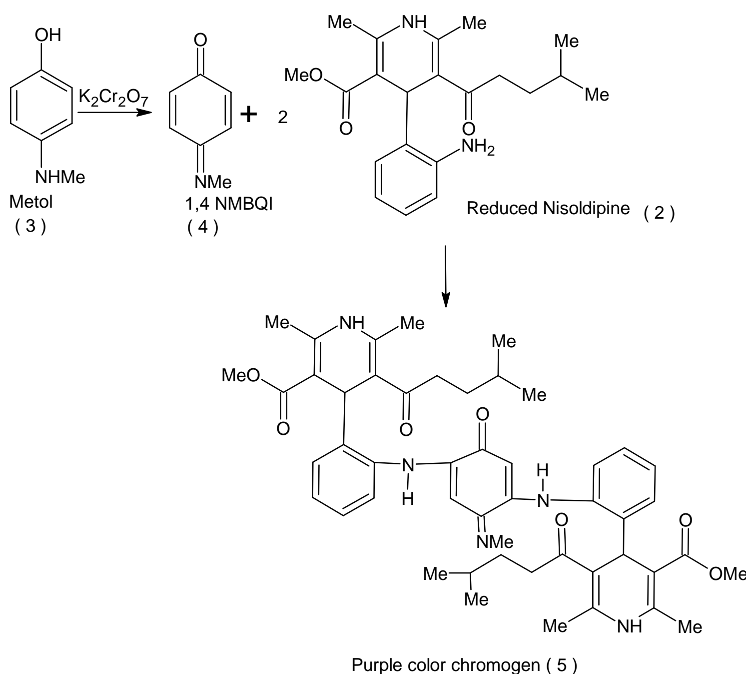

Figure 3: Scheme 2

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).

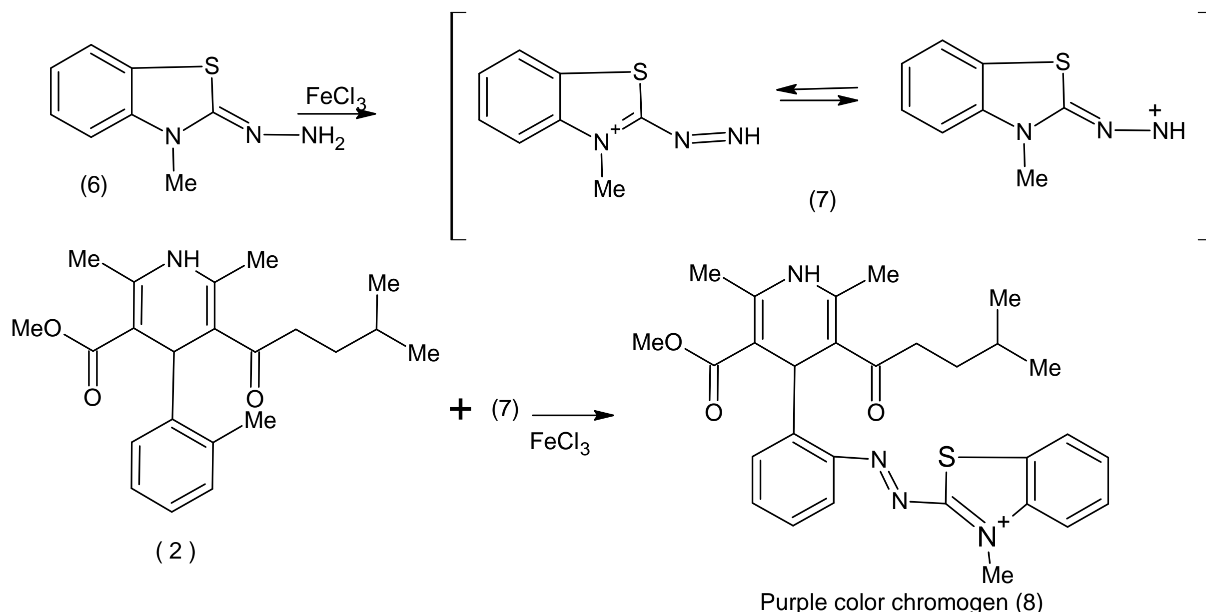

Figure 4: Scheme 3

Table 1: Optical Characteristics and Linearity Parameters

Optical Characteristics	METOL (Method A)	MBTH (Method B)
λ_{max}	520	623
Beer's law limits (mg/ml)	5-30	40-240
Molar absorptivity (L/mol.cm)	1.389×10^3	1.348×10^2
Sandell's sensitivity (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 l_{max}		
** For six measurements.		

Table 2: Accuracy Studies (% Recovery)

	Labeled Amount (µg)	Amount Added (µg)	% Recovery	RSD
Method A	20	16	99.4231 ± 0.7025	0.4074
	20	20	99.1244 ± 0.7017	0.4102
	20	24	99.3543 ± 0.7026	0.3628
Method B	20	16	99.3231 ± 0.7026	0.3052
	20	20	99.2241 ± 0.7027	0.4136
	20	24	99.1641 ± 0.7019	0.4151

Table 3: Precision Studies (Intra-day precision)

	Concentration (µg/ml)	% Drug Content	Mean RSD
Method A	10	99.958 ± 0.7874	0.48225
	20	99.928 ± 0.1014	
	30	99.297 ± 1.114	
Method B	10	99.3231 ± 0.7026	0.4662
	20	99.2241 ± 0.7027	
	30	99.1641 ± 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.

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REFERENCES

[1] Knorr, A. M., Why is nisoldipine a specific agent in ischemic left ventricular dysfunction?, *Am. J. Cardiol*., **1995**, 75(13), 1, 36-40.
[2] Likussar, W., Michelitsch, A., Asilavecz, M. S., Determination of nisoldipine in film tablets by different pulse polarography, *Monatsh. Chem*., **1994**, 125, 509-513.
[3] Dogrukol, A. K. D., Gokoren, N., Tuncel, M., A differential pulse voltametric determination of nisoldipine using glassy carbon electrode in pharmaceutical preparations, *Anal. Lett*., **1998**, 31(1), 105-116.
[4] Gupta, A., Ram, S., Gaud, A., Ganga, S., High performance thin liquid chromatographic method for determination of nisoldipine from pharmaceutical samples, *J. Chem*., **2010**, 7(3), 751-756.
[5] Agbaba, D., Vucicevic, K., Marinkovic, V., Determination of nisoldipine and its impurities in pharmaceuticals, *Acta. Chromatogr*., **2004**, 60(3-4), 223-227.
[6] Wang, H., Zhang, L., Qiao, W., Zhifang, Y., Min, Li., Validated LC-MS-MS method for determination of m-nisoldipine polymorphs in rat plasma and its applications to pharmacokinetic studies, *J. Chromatogr. B*., **2006**, 835(1-2), 71-76.
[7] Marques, M. P., Santos, N. A. G., Coelho, E. B., Bonato, P. S., Lanchote, V. L., Enantioselective assay of nisoldipine in human plasma by chiral high-performance liquid chromatography combined with gas chromatographic-mass spectrometry, *J. Chromatogr. B. Biomed. Sci. Appl*., **2001**, 762, 87-95.
[8] Marinkovic, V. D., Agbaba, D., Rajic, K. K., Vladimirov, S., Nedeljkovic, J. M**.,** Photochemical degradation of solid-state nisoldipine monitored by HPLC, *J. Pharm. Biomed. Sci*., **2003**, 32, 929-935.
[9] Safhi, M. M., Novel spectrophotometric method for the estimation of nisoldipine in bulk and pharmaceutical dosage forms, *Der. Pharmacia. Chem*., **2011**, 3(4), 275-278.
[10] Abdulla, S. A., El-Shal, M. A., Attia, A. K., Validated HPLC method for the determination of nisoldipine, *Pharm. Anal. Acta*., **2013**, doi:10.4172/2153-2435, S1-004.
[11] Nagaraj, M. Y., Safhi, M. M., Rapid RP-HPLC method for estimation of nisoldipine from tablet dosage form, *Der. Pharmacia. Sinica*., **2011**, 2(6), 122-126.
[12] Safhi, M. M., Development and validation of spectrophotometric methods for the estimation of nisoldipine in tablets, *J. Chem. Biol. Phys. Sci*., **2015**, 5(3), 2319-2327.
[13] Niraimathi, V., Jerad, S. A., Nanjappan, K., Kokila, R., Latha, T., Spectrophotometric estimation of nisoldipine in bulk and tablet formulations, *Res. J. Pharm. Technol*., **2011**, 4(5), 762-763.
[14] Al-Bratty, M., Extractive spectrophotometric determination of nisoldipine by ion-pair complex formation, *Int. J. Biol. Pharm. Allied. Sci*., **2016**, 5(1), 1-7.
[15] Honda, S., Nishimura, Y., Chiba, H., Kakehi, K., Determination of carbohydrates by condensation with 3-methyl-2-benzothiazolinonehydrazone, *Anal. Chim. Acta*., **1981**, 131, 293-296.
[16] Hünig, S., Balli, H., Quast, H., Penta(aza)-pentamethine cyanine dyes, *Angew. Chem. Int. Ed. Engl*., **1962**, 1(1), 47.
[17] Hünig, S., Balli, H., Breither, E., Brühne, F., Geiger, H., Grigat, E., Müller, F., Quast, H., Heterocyclic azo dyes by oxidative coupling, *Angew. Chem. Int. Ed. Engl*., **1962**, 1, 640-646.
[18] Hünig, S., Quast, H., Pentaaza-pentamethincyanine, *I. Justus. Liebigs. Ann. Chem*., **1968**, 711, 139-156.

[19] Hünig, S., Balli, H., Fritsch, K. H., Herrmann, H., Köbrich, G., Werner, H., Grigat, E., Müller, F., Nöther, H., Oette, K. H., Heterocyclische azofarbstoffe durch oxydative kupplung, *Angew. Chem. Weinheim. Bergstr. Ger*., **1958**, 70, 215-222.
[20] Hünig, S., Oxidative coupling: A new approach to azo chemistry, *J. Chem. Educ*., **1969**, 46(11), 734.
[21] Bartsch, R. A., Hünig, S., Quast, H., Mechanism of oxidation of 3-methyl-2-benzothiazolinonehydrazone hydrochloride by potassium ferricyanide in aqueous methanol, *J. Am. Chem. Soc*., **1970**, 92, 6007-6011.
[22] Gasparic, J., Svobodova, D., Pospisilova, M., Identification of organic compounds. Part LXXXVI. Investigation of the color reaction of phenols with the MBTH (3-methyl-2-benzothiazolinone hydrazone hydrochloride) reagent, *Mikrochim. Acta*., **1977**, 1, 241-250.
[23] Hünig, S., Balli, H., Azofarbstoffe durch oxydative kupplung, X: Kupplungsaktivität heterocyclischer N-methyl-2-hydrazone gegenüber phenol, *Justus. Liebigs. Ann. Chem*., **1959**, 628, 56-68.