WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 5, 1066-1074. Research Article ISSN 2277– 7105

DEVELOPMENT AND VALIDATION OF FIRST ORDER DERIVATIVE METHOD FOR THE SIMULTANEOUS ESTIMATION OF TELMISARTAN AND NIFEDIPINE IN SYNTHETIC MIXTURE

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Article Received on
01 March 2016,
Revised on 22 March 2016,
Accepted on 13 April 2016
DOI: 10.20959/wjpr20165-6120

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ABSTRACT

A first order derivative spectrophotometry method is developed for the simultaneous determination of Telmisartan (TEL) and Nifedipine (NIF) in synthetic mixture. This method is simple, precise, accurate and economical. The work was carried out on Shimadzu model 1800 (Japan) double beam UV visible spectrophotometer with spectral width of 2 nm, wavelength accuracy of 0.5 nm and a pair of 10 mm matched quartz cell was used to measure absorbance of all the solutions. Distilled methanol was used as a solvent. The linearity range for both the drugs TEL and NIF were 1-18µg/ml and 2-20µg/ml. The spectra of the drug were converted to the first derivative forms and the ZCP's (Zero Crossing Points) were obtained. The absorbance of the TEL was measured at 235.7nm (ZCP of NIF) and for the NIF was measured at 252.1 nm (ZCP of TEL). The results of the analysis of synthetic mixture by the proposed method is highly reproducible and reliable and it is in good agreement with the label claim of the drug. This method can be used for the routine analysis of the TEL and NIF in synthetic mixture without any interference of excipients.

KEYWORDS: Telmisartan (TEL), Nifedipine (NIF), First order derivative spectrophotometry, Synthetic mixture, Validation, ICH Guidelines, Recovery.

INTRODUCTION

Telmisartan (TEL) is an angiotensin II receptor antagonist (angiotensin receptor blocker, ARB) used in the management of hypertension. It was discovered by Boehringer Ingelheim and launched in 1999 as Micardis. It is essentially used in the treatment of essential hypertension. The IUPAC name of TEL is 2-(4- methyl-6-{1-methyl-1H-1, 3-benzodiazol-2-yl}-2-propyl-1H-1, 3- Benzodiazol-1-yl] methyl} Phenyl} benzoic acid. The usually effective dose TEL is 40-80 mg once daily and dose can be increased to a maximum of 80 mg once daily. It is contraindicated during pregnancy. TEL is official in Indian Pharmacopeia[2] and United State Pharmacopeia[3], British Pharmacopeia.[4] Literature survey reveals that HPLC[6], UV Spectrophotometry[7], and HPTLC[12] methods for determination of TEL in single as well as in combination with other drugs for pharmaceutical dosage forms. NIF is the calcium channel blocker medication which is used to manage angina, high blood pressure, Raynaud's phenomenon and premature labor. NIF was discovered in 1969 and approved for use in the United State in 1981. The IUPAC name of NIF is 3, 5-dimethyl 2, 6-dimethyl-4-(2-nitrophenyl)-1, 4-dihydropyridine-3, 5-dicarboxylate. It is available in 10mg, 20 mg, 30 mg, 60mg, and 90 mg strength. NIF is official in Indian Pharmacopeia[13], British Pharmacopeia[14], United State Pharmacopeia[15], Japanese Pharmacopeia[16], and European Pharmacopeia[17]. Literature survey reveals that UV Spectrophotometry[18], HPTLC[20], HPLC[22] methods for determination of NIF in single as well as in combination with other drugs for pharmaceutical dosage forms. Literature survey reveals only one reported spectrophotometric method for simultaneous estimation of TEL and NIF in synthetic mixture. The combination of these two drugs is not official in any pharmacopeias. When the NIF with low dose is combined with the TEL provides a greater and earlier clinic and ambulatory BP reduction than the other combination or in monotherapy[5]

MATERIALS AND METHODS

Reagents and Materials

TEL and NIF bulk powder was kindly provided by Zydus Cadila, Gujarat, India. Methanol AR Grade was procured from S. D. Fine Chemicals Ltd., Mumbai, India. What man filter paper no 41 (Millipore, USA) was also used in the study.

Apparatus

A Shimadzu model 1800 (Japan) double beam UV/Visible spectrophotometer with spectral width of 2 nm, wavelength accuracy of 0.5 nm and a pair of 10 mm matched quartz cell was

used to measure absorbance of all the solutions. Spectra were obtained by UV-Probe system software. A Sartorius CP224S analytical balance (Gottingen, Germany), an ultrasonic bath (Frontline FS 4, Mumbai, India) was used in the area of study.

Preparation of standard stock solutions

Weigh accurate quantity of TEL (10 mg) and NIF (10mg). The quantity were transferred to a separate 100 ml volumetric flask. Dissolved and shake the drug properly and mitigated up to the mark with distilled methanol to obtain standard solution having concentrations of TEL (100µg/ml) and NIF (100µg/ml).

Preparation of synthetic mixture

Preparation of Synthetic mixture (300 mg) was done by using TEL (80 mg), NIF (20 mg) and excipients (200 mg) like Magnesium stearate, Lactose and Talc.

Development of method

Weight accurate quantity of TEL and NIF and solution of TEL and NIF were prepared separately in distilled methanol to a concentration of 10µg/ml. The wavelength range selected for their scanning were 200-400 nm. 1 nm interval was selected for the recording of data. The first order derivative spectra were obtained from the spectra of the two drugs. The one wavelength was selected where one drug showed zero crossing and where the other drug show substantial absorbance by observing the overlain first derivative spectra. The wavelength selected for Telmisartan was 252.1 nm where NIF shows absorbance and the wavelength selected for NIF was 235.7 nm where the TEL shows absorbance. Hence the selected analytical wavelength were 252.1 nm and 235.7 nm for determination of NIF and TEL without any interference from the other drug in their synthetic mixture.

METHOD VALIDATION

The proposed method was validated as per the International Conference on Harmonization (ICH) guidelines.[24]

Linearity (Calibration curve)

Weight accurate quantity of TEL and NIF and prepare appropriate standard working solutions of TEL (0.1,0.2,0.4,0.6,0.8,1.0,1.2,1.4,1.6,1.8ml) and for NIF (0.2,0.4,0.6,0.8,1.0,1.2,1.4,1.6,1.8,2.0 ml). The concentration range selected for TEL was 1-18 µg/ml) and for NIF was 2-20 µg/ml and calibration curves were plotted accordingly. The

standard working solutions of TEL and NIF were transferred to a series of 10 ml of volumetric flasks and diluted to the mark with distilled methanol. First derivative absorbance was measured at 252.1 nm for NIF and 235.7 nm for TEL. The calibration curves were constructed by plotting absorbance Vs concentration.

Precision

The precision of the method was verified as repeatability, intra-day, inter-day and reproducibility. The Repeatability was performed by repeating 6 times the sample solution of 10µg/ml for TEL and NIF drug. The precision of the instrument was checked by repeated scanning and measurement of absorbance of solution (n=6) for TEL and NIF (10µg/ml) without changing the parameter of the first-derivative spectrophotometry method. The three different concentrations of standard solutions of TEL and NIF (8, 10, 12µg/ml) were used three times on the same day or three different days in a period of seven days. In this way the intraday and interday precision of the method was determined. The results were mentioned in the relative standard deviation (% RSD).

Accuracy

Accuracy is the measure of exactness of an analytical method, or the closeness of agreement between the measured value and the accepted reference value. The accuracy of the method was determined by standard addition method. The recovery was performed by adding known amounts of standard solutions of TEL and NIF at 80%, 100%, and 120% level to prequantified sample solution of TEL (8µg/ml) and NIF (2µg/ml). The experiment was repeated three times.

Limit of detection (LOD) and Limit of quantification (LOQ)

The LOD and LOQ of the drugs were calculated as $3.3\times\sigma/s$ and LOQ = $10\ \sigma/s$ where, σ = the standard deviation of the response & S= Slope of the calibration curve.

Analysis of TEL and NIF in synthetic Mixture

An accurate amount of standard drug powder TEL (80 mg) and NIF (20 mg) were weighted. The response of the sample solution was measured at 252.1nm and 235.7nm for quantitation for NIF and TEL, respectively. The amounts of the TEL and NIF present in the sample solution were calculated by fitting the responses into the regression equation for TEL and NIF in the proposed method.

RESULTS AND DISCUSSIONS

The UV range is selected for the scanning of the standard solution of TEL and NIF (200-400nm). The first order derivative spectra were obtained by processing the Zero-order spectra. The derivative spectra showed absorbance at 252.1 nm (ZCP of TEL) for NIF and 235.7 nm (ZCP of NIF) for TEL. The absorbances were recorded at these wave-lengths by first order derivative method. The good quantitative determination of both drugs is carried out by first derivative spectra at their respective ZCPs without any inter ference. The first-order spectra give satisfactory ZCPs and good quantitative determi-nation of both drugs without any interference so there is no requirement for the testing of second and third ordered spectra.

Table 1: Recovery data for proposed method

Drug	Level	Amount taken (µg/ml)	Amount added (%)	% Mean recovery ± S.D. (n = 3)
TEL	I	8	80	100.32 ±0.72
	II	8	100	99.74 ± 0.62
	III	8	120	100.78 ± 0.68
NIF	I	2	80	99.98 ±0.91
	II	2	100	100.46 ±0.78
	III	2	120	99.78± 0.99

S. D. is Standard deviation and n is number of replicate

Table 2: Analysis of TEL and NIF by proposed method

Synthetic mixture	Label claim (mg)		Amount found (mg)		% Label claim ± S. D. (n = 5)	
	TEL	NIF	TEL	NIF	TEL	NIF
I	80	20	80.03	20	100.37	100

S. D. is Standard deviation and n is number of replicate

Table 3: Regression analysis data and summary of validation parameter for the proposed method

Parameters	First-derivative UV Spectrophotometry	
	TEL at 235.7 nm	NIF at 252.1 nm
Concentration range (µg/ml)	1-18	2-20
Regression equation Slop (m) Intercept (c)	Y=0.0065× - 0.0135 0.0065 0.0135	Y= = 0.0015x + 0.0011 0.0015 0.0011
Correlation coefficient (r^2)	0.995	0.996
LOD (µg/ml)	0.94	1.85
LOQ (µg/ml)	2.85	5.62
Accuracy (recovery, n=3) %	100.28 ± 0.67	100.07±0.89

Repeatability (RSD, n=6)%	1.72	1.08
Precision (RSD)% Interday Intraday	 0.94-1.79 0.90-1.68	 0.69-1.20 0.70-1.24

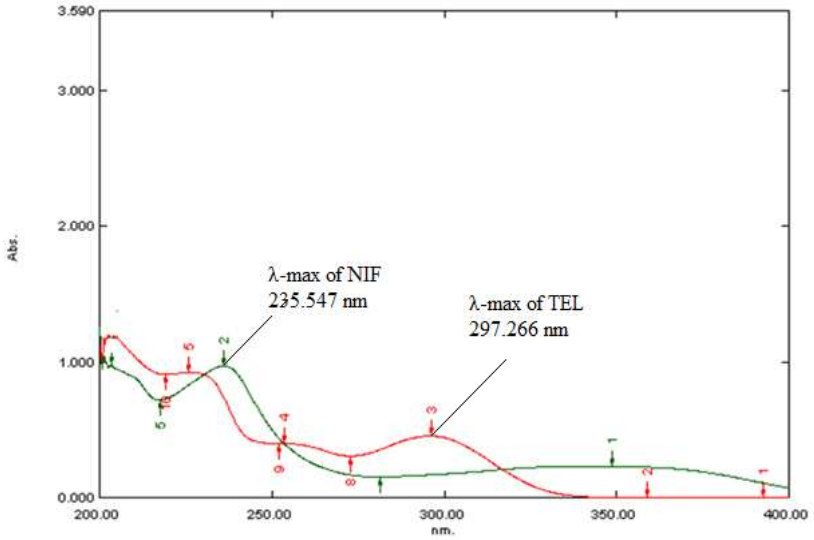

Figure.1: Overlain absorption spectra of standard solution of TEL (8 µg/ml) and NIF (12 µg/ml) in distilled methanol

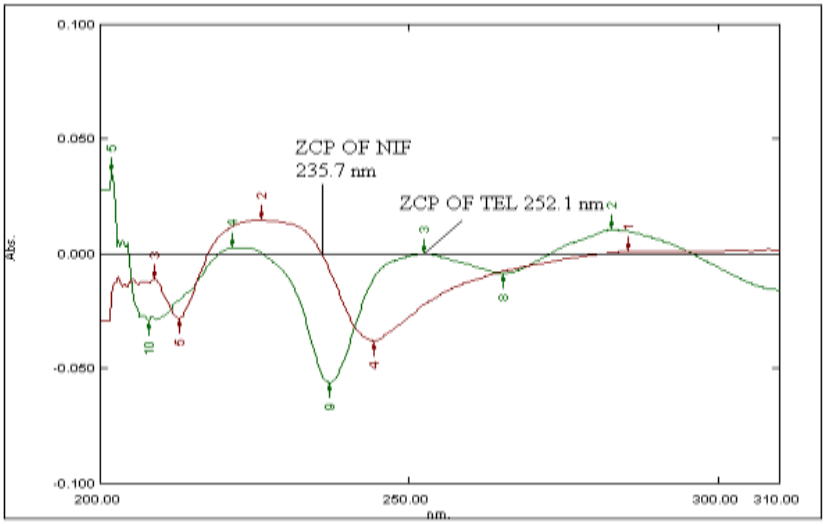

Figure.2: Overlain absorption first derivative spectra of standard solution of TEL (8 µg/ml) and NIF (12 µg/ml) in distilled Methanol.

CONCLUSION

The data obtained from the analysis of first order derivative spectrophotometry concludes that the method has linear response in the concentration range of 1-18µg/ml for TEL and 2-20µg/ml for NIF respectively with coefficient of correlation (r2) = 0.995 and (r2)= 0.996 for

TEL and NIF, respectively. The results of the analysis of synthetic mixture by the proposed method is highly reproducible and reliable and it is in good agreement with the label claim of the drug. This method can be used for the routine analysis of the TEL and NIF in synthetic mixture without any interference of excipients.

ACKNOWLEDGEMENT

The authors are thankful to Zydus Cadila, Ahmedabad, and Gujarat, India for providing gift sample of TEL and NIF for research. The authors are highly thankful to Shree S. K. Patel College of Pharmaceutical Education & Research, Ganpat University, Ganpat Vidyanagar, Mehsana, Gujarat, India for providing all the facilities to carry out the work.

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