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Research Article

DEVELOPMENT AND VALIDATION OF SIMULTANEOUS EQUATION METHOD FOR SIMULTANEOUS ESTIMATION OF TELMISARTAN AND NIFEDIPINE IN SYNTHETIC MIXTURE

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ABSTRACT

This method deals with the simultaneous determination of the Telmisartan and Nifedipine in the 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 Telmisartan and Nifedipine were 1-18µg/ml and 2-20µg/ml. The Telmisartan has absorbance maxima at 297.2 nm and Nifedipine has absorbance maxima at 235.5 nm in distilled methanol. The mean recovery was 100.7±0.64 for Telmisartan and 100.3±0.77 for Nifedipine respectively. The results of analysis have been validated statically and by recovery studies. This simple and precise method can be used for routine analysis of both the drugs in quality control laboratories.

Keywords: Telmisartan, Nifedipine, Simultaneous Equation Method, Spectrophotometric, 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 (10 mg) and transfer them to different 100 ml volumetric flask and mitigate up to the mark with distilled methanol. Standard solution having concentration of (100µg/ml) for both the drugs were obtained.

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

When sample contains two absorbing drugs **(**A and B**)** each of which absorbs at the λmax of the other It may be possible to determine both drugs by the method of simultaneous equation by obtaining following information like absorptivity of A at λ_1 and λ_2 a_x1 and a_x2 and absorptivity**'**s of B at λ_1 and λ_2, a_y1 and a_y2 and absorbance of the diluted sample at λ_1 and λ_2, A_1 and A_2 respectively**.** The standard solution of TEL and NIF were prepared separately in distilled methanol at a concentration of 10µg/ml**.** Nine standard solutions having concentration **(**1,2,4,6,8,10,12,14,16,18 µg/ml**)** for TEL and **(**2,4,6,8,10,12,14,16,18,20 µg/ml**)** for NIF were prepared in distilled methanol using the standard solutions**.** They were scanned in the wavelength range of 200-400 nm**.** Maximum absorbance was obtained at 297**.**2 nm for TEL and 235**.**5nm for NIF**.** The concentration of TEL and NIF in a sample solution was determined by solving the respective simultaneous equations generated by using absorptivity coefficients and absorbance values of TEL and NIF at these wavelengths**.**

$Cx = (A_2\ aY_1 - A_1\ aY_2) / (aY_1\ aX_2 - aY_2\ aX_1)$ ..... **(**1**)**

$CY = (A_1\ ax_2 - A_2\ ax_1) / (aY_1aX_2 - aY_2\ aX_1)$..... **(**2**)**

Where, A_1 and A_2 are absorbance of mixture at 297**.**2 and 235**.**5 and aX_1 and aY_1 are absorptivity**'**s of NIF and TEL at 235**.**5 nm; aX_2 and aY_2 are absorptivity**'**s of NIF and TEL, respectively at 297**.**2

METHOD VALIDATION

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

Linearity (Calibration curve)

Linearity should be determined by using a minimum of six standards whose concentration span 80-120% of the expected concentration range. The calibration curves were plotted in a concentration range of 1-18µg/ml for TEL and 2-20 µg/ml for NIF. Afterwards standard stock solution of TEL and NIF in the range of (0.1,0.2,0.4,0.6,0.8,1.0,1.2,1.4,1.6,1.8 ml) and (0.2,0.4,0.6,0.8,1.0,1.2,1.4,1.6,1.8,2.0) were transferred to a separate 10 ml volumetric flask and mitigated up to the mark with distilled methanol for both the drugs respectively. The absorbance of solutions were measured at 297.2 and 235.5 nm. The calibration curves were constructed and linear regression equations were calculated for the drugs.

Precision

Repeatability:
Repeatability refers to the results of the method operating over a short time interval under the same conditions. An appropriate volume of standard solution of TEL and NIF were prepared. The absorbance was measured by UV Spectrophotometer six times on the same day without changing the parameters of the developed method and % RSD was calculated.

Intraday and interday precision:
The intraday variation (% RSD) was determined by the analysis of three standard solutions of TEL and NIF three times on the same day.
Interday variation was determined by analysis of three standard solutions of TEL and NIF three times on the three different days for period of one week.

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 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 **(**8 µg/ml**)** and NIF **(**2µg/ml**).** The amounts of TEL and NIF were calculated by putting obtained values in the equations **(**1**)** and **(**2**).** The recovery study analysis was repeated three times and average recoveries were calculated**.**

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

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

Determination of TEL and NIF in synthetic Mixture

The accurate amount equivalent to 80mg TEL and 20mg NIF from synthetic mixture and it was transferred to 100 ml volumetric flask**.** To it add 50ml of distilled methanol and sonicate it for 15 minutes**.** Then filtration of the solution was carried out by what man filter paper No 41 and volume was mitigated up to the mark with distilled methanol**.** The resulting solution was suitably mitigated with distilled methanol and get the final concentration of 8µg/ml for TEL and 2µg/ml for NIF**.** The absorbance of the sample solution were recorded at 297**.**2 nm and 235**.**5 nm i**.**e**.**A_1 and A_2 respectively and ratios of the absorbance were calculated A_2/A_1**.**Relative concentration of both the drugs in the synthetic mixture was calculated using equation **(**1**)** and **(**2**).**

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	100.66±0.57
	II	8	100	100.33 ± 1.01
	III	8	120	100.10 ± 0.47
NIF	I	2	80	99 ± 1
	II	2	100	101.33 ± 0.28
	III	2	120	100.21 ± 0.96

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

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	20.3	100.6 ± 1.22	100.3 ± 4.04

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

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

Parameters	TEL		NIF	
Wavelength (nm)	297.2	235.5	297.2	235.5
Beer's law limit (µg /ml)	1-18	1-18	2-20	2-20
Regression equation (y = a + bc) Slope (b) Intercept (a) 	y = 0.0553x+ 0.0047 0.0553 0.0047	y = 0.0905x+ 0.0195 0.0905 0.0195	y= 0.0074x- 0.013 0.0074 0.013	y= 0.0768x- 0.0675 0.0768 0.0675
Correlation coefficient (r^2)	0.998	0.997	0.997	0.996
LOD (µg/ml)	0.14	0.11	0.38	0.09
LOQ (µg /ml)	0.44	0.35	1.16	0.28
Repoeatability (% RSD, n = 6)	1.86	1.12	1.71	0.74
Precision (% RSD, n = 3) Interday Intraday	 0.26-0.35 0.51-0.55	 0.32-0.93 0.51-1.79	 1.65-1.95 0.95-1.42	 0.85-1.18 0.54-0.96
Accuracy (% recovery, n = 3)	100.7 ± 0.64		100.3 ± 0.77	

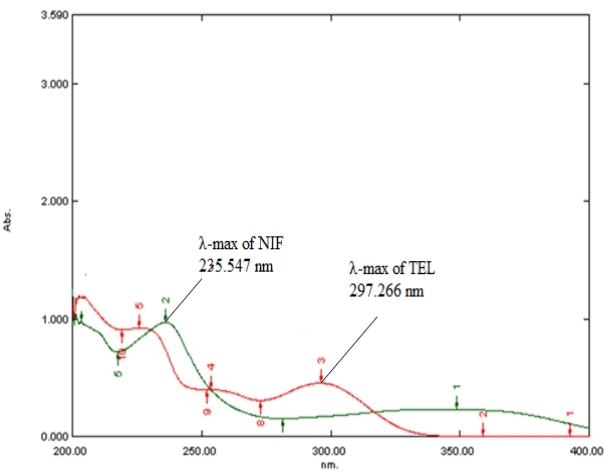

Figure: 1 Overlain Spectra of TEL (8 µg/ml) and NIF (12µg/ml) in distilled methanol

RESULTS AND DISCUSSIONS

In this method, two wavelengths were used. For the analysis of the drugs 297.2 nm (λmax of TEL) and 235.5 nm (λmax of NIF) are the wavelengths at which calibration curves were prepared for both the drugs. These drugs comply with the beer's law at all the wavelengths and obeys the linearity in the concentration range of 1-18µg/ml for TEL and 2-20µg/ml for NIF The linearity of the calibration curve was validated by the high values of correlation coefficient of regression. Characteristic parameters of regression equation and correlation are given in (Table 3). Relative standard deviation was less than 2 %, which indicates that proposed method is repeatable. The validated parameters were studied at all the selected wavelengths for this developed method which were found be within acceptable limits. The accuracy was determined at 80%, 100%, 120% level which gives good mean percentage recovery. The recovery experiment was performed by the standard addition method. The mean recoveries were 100.7 ± 0.64 and 100.3 ± 0.77 for TEL and NIF respectively indicates accuracy of the proposed method. (Table 1) The precision was studied as repeatability, intraday, and interday variations (%RSD >2) for both the drugs. The results obtained are in good agreement with the corresponding labeled amount. (Table 2).This method was quite simple, rapid, accurate, precise and sensitive by observing the validation parameters. This method can be used for analysis of TEL and NIF in synthetic mixture

CONCLUSION

The developed simultaneous equation method was used for the simultaneous determination of TEL and NIF which was found to be simple, precise and accurate. The low cost solvent like distilled methanol was used for this method. On the basis of the validation data this method can be used in future for the formulation.

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