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Development and Validation of Dual Wavelength Spectrophotometric Method for Simultaneous Estimation of Telmisartan and Nifedipine in Synthetic Mixture

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ABSTRACT

A simple, sensitive, accurate, precise, and economical dual wavelength method was developed which was used for simultaneous determination of Telmisartan and Nifedipine. The importance of dual wavelength method was used to estimate components of interest which are of unknown concentration. The distilled methanol was used as a solvent. The theory of dual wavelength method is ‘’the absorbance difference between two points on the mixture spectra is directly proportional to the concentration of the component of interest’’. The Nifedipine was determined directly at 346.5nm in distilled methanol. The wavelengths selected for determination of Telmisartan were 346.5nm and 264.5nm in distilled methanol. The concentration range for Telmisartan and Nifedipine was found to be 1-18 µg/ml and 2-20 µg/ml and it shows good correlation. The accuracy and precision were found to be within the limits. Here no interference of excipients was found and it is successfully applied to any pharmaceutical dosage form. The results of analysis were validated.

INTRODUCTION

Telmisartan (TEL) is chemically 2-(4- methyl-6-{1-methyl-1H-1, 3-benzodiazol-2-yl}-2-propyl-1H-1, 3- Benzodiazol-1-yl] methyl} Phenyl} benzoic acid. It was discovered by Boehringer Ingelheim and launched in 1999 as Micardis. TEL is an angiotensin II receptor antagonist (angiotensin receptor blocker,ARB) used in the management of hypertension. It is essentially used in the treatment of essential hypertension. The usually effective dose of TEL is 40-80mg once daily and dose can be increased to a maximum of 80mg once daily. It is contraindicated during pregnancy. TEL is official in Indian Pharmacopeia[2], United State Pharmacopeia[3] and 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. Nifedipine (NIF) is the calcium channel blocker medication which is used to manage angina, high blood pressure, Raynaud's phenomenon and premature labor. The NIF is chemically 3, 5-dimethyl 2, 6-dimethyl-4-(2-nitrophenyl)-1, 4-dihydropyridine-3, 5-dicarboxylate.NIF was discovered in 1969 and approved for use in the United State in 1981. It is available in 10mg, 20mg, 30mg, 60mg, and 90mg strengths. 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 HPLC[18], HPTLC[19], UV Spectrophotometry [20] 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 powders were kindly provided by Zydus Cadila, Gujarat, India. Methanol AR Grade was procured from S. D. Fine Chemicals Ltd., Mumbai, India. Whatman filter paper no 41 (Millipore, USA) was also used in the area of this study.

Apparatus

The apparatus Shimadzu model 1800 (Japan) double beam UV/Visible spectrophotometer is used which is having spectral width of 2nm and wavelength accuracy was found to be 0.5nm. The absorbances of all the solutions were measured by pair of 10mm matched quartz cell. Spectra were obtained by UV-Probe 2.0 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 an accurate amount of TEL(10mg) and NIF (10mg) to a different 100 ml volumetric flask and mitigated it up to the mark with distilled methanol to obtain standard solution having concentrations of 100µg/ml for both drugs. For NIF preparation amber colored volumetric flask was used.

Preparation of synthetic mixture

Synthetic mixture was prepared by using TEL (80mg) and NIF (20mg) and excipients (200mg) like starch, magnesium stearate, lactose and talc.

Methodology

The component of unknown concentration is estimated by the dual wavelength method. It is basically the absorbance difference between two points on the mixture spectra is directly proportional to the concentration of the component of interest. The utility of dual wavelength data processing program is its ability to calculate unknown concentration of component of interest in a mixture containing an interfering component. From the overlain spectra of two drugs (Figure 1), it is the confirmation of the direct determination of NIF at 346.5nm in distilled methanol. (No absorbance of TEL found at 346.5nm). The TEL is determined by selecting two wavelengths (346.5nm & 264.5nm) where NIF shows same absorbance. The estimation of TEL is carried out subtracting absorbance due to NIF at 264.5nm and the difference between 264.5 and 346.5nm is directly proportional to the concentration of TEL in the mixture.

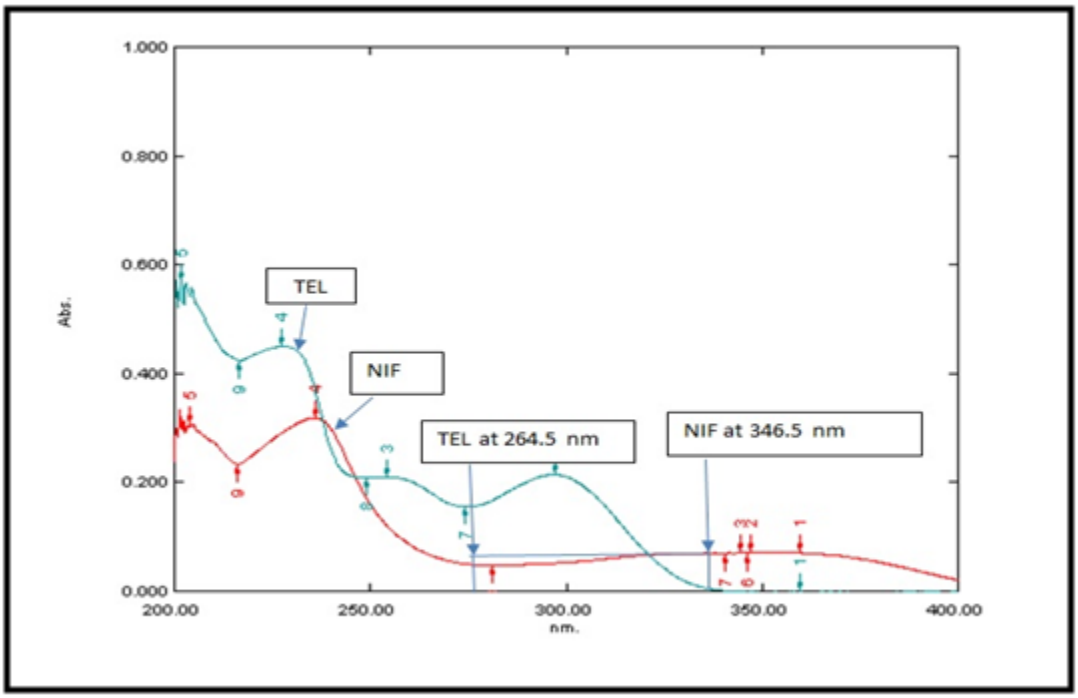

Figure 1: Overlain zero order absorption spectra of TEL and NIF in distilled methanol

METHOD VALIDATION

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

Linearity

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, 2.0ml) were transferred to a separate 10 ml volumetric flask and diluted up to the mark with distilled methanol for both the drugs respectively. The absorbance of the solution was measured at 264.5nm and 346.5nm. By plotting the absorbance versus concentration the calibration curves were plotted and regression equations were calculated for drugs.

Precision (Repeatability)

An appropriate volume of standard solution of TEL and NIF were prepared. The precision of the instrument was checked by repeated scanning & by measuring the absorbance of the solutions

(n=6) of TEL and NIF (10 µg/ml for both drugs) without changing the parameters of the proposed method. The results were reported in terms of relative standard deviation (%RSD).

Intermediate precision (Reproducibility)

Three different concentrations of standard solutions of TEL and NIF 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 (% Recovery study)

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 amounts of TEL and NIF were estimated by putting obtained values in the regression line equation. The experiment was repeated three times.

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

According to the International Conference on Harmonization (ICH) guidelines calculating the signal-to-Noise ratio (LOD) and (LOQ) of the drug were obtained.

$$LOD = 3.3 \times \sigma/S$$

$$LOQ = 10 \times \sigma/S$$

Analysis of TEL and NIF in synthetic mixture

An accurate amount of standard drug powder TEL (80mg) and NIF (20mg) were weighed. The formulation additives used in this study are starch, lactose, magnesium stearate and talc. The synthetic mixture was then transferred to 100 ml volumetric flask containing 50 ml methanol and sonicated for 15 minutes. Filtration of the solution occurs through Whatman filter paper No.41 and volume was mitigated up to the mark with distilled methanol. The final concentration of

8µg/ml for TEL and 2 µg/ml for NIF. The absorbance of the sample solution was measured against methanol as blank at 264.5nm and 346.5nm for quantification of TEL and NIF. The amount of TEL and NIF present in the sample solutions were determined by putting obtained values in respective regression equation for TEL and NIF.

RESULTS AND DISCUSSION

This method uses two specific wavelengths. First wavelength λ_1 is the one which shows minimum absorbance of NIF and at this wavelength the TEL drug does not interfere (346.5nm). Second wavelength λ_2 was the wavelength at which the absorbance of the NIF was same as at λ_1. And TEL was also having some absorbance at this wavelength (264.5nm). The absorbance of the NIF was found to be the equal at both of these wavelengths. The concentration of the TEL was determined from the mixture of NIF and TEL by this two selected wavelengths. The difference in absorbance at these two wavelengths ($A_{264.5}$ –$A_{346.5}$) cancels out the contribution of absorbance of NIF in mixture. The linearity range for both the drugs were found to be 1-18µg/ml for TEL and 2-20µg/ml for NIF. Characteristics parameters of regression equation and correlation are given in (Table 1). The precision was calculated as a repeatability (%RSD) and intraday and interday variation (%RSD) for both drugs. Accuracy was performed by recovery (Table 2). The sensitivity of the method was found by the LOD and LOQ which were found to be 0.06 and 0.2µg/ml for TEL and 0.12 And 0.39µg/ml NIF. The amounts of TEL & NIF present in synthetic mixture were determined by this method. The results obtained are in good agreement with the corresponding labeled amount (Table 3). The method was found to be sensitive, accurate, precise, and economical by observing the validation parameters. Hence, the method can be employed for the routine analysis of these drugs in combinations.

Table 1: Regression analysis data and summary of validation parameters for the proposed method

PARAMETERS	TEL	NIF
Wavelength range (nm)	264.5 and 346.5	346.5
Beer's law limit (µg/ml)	1- 18	2 -20
Regression equation (y = a+bc) Slope (b) Intercept (a)	0.045x + 0.001 0.045 0.001	0.0121x + 0.003 0.0121 0.003
Correlation Coefficient (r^2)	0.9991	0.9977
Method precision (Repeatability) (% RSD), (n = 6)	0.19	1.29
Intraday (n = 3) (%RSD)	0.28– 0.35	0.78 – 1.27
Interday (n = 3) (%RSD)	0.39 – 0.44	1.09 –1.41
LOD (µg/ml)	0.06	0.12
LOQ (µg/ml)	0.2	0.39
Accuracy (Mean % Recovery ± S.D.) (n =3)	100.69± 0.69	100.83 ± 1.12
% Assay ± S.D. (n = 5)	100.79 ± 0.64	101.4 ± 0.41

RSD = Relative standard deviation. LOD = Limit of detection. LOQ = Limit of quantification. SD = Standard deviation.

Table 2: Recovery data of proposed method

Drug	Level	Amount taken (µg/ml)	Amount added (%)	% Mean recovery ± S.D. (n = 3)
TEL	I	8	80	100.5 ± 0.50
	II	8	100	100.2 ± 0.54
	III	8	120	100.3 ± 62
NIF	I	2	80	98.5 ± 0.60
	II	2	100	100.2 ± 0.52
	III	2	120	100.3 ± 0.42

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

Table 3: 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	80.2	20.2	100.2 ± 0.55	100.4 ± 1.68

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

CONCLUSION

The dual wavelength spectrophotometric method was found to be simple, sensitive, accurate, precise and economical and can be used for the routine analysis of these two drugs in combined synthetic mixture.

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