ISSN: 0975-766X
CODEN: IJPTFI
Available Online through
www.ijptonline.com
Research Article

SIMULTANEOUS SPECTROPHOTOMETRIC ESTIMATION OF TELMISARTAN AND METOPROLOL SUCCINATE IN BULK AND TABLET DOSAGE FORMS

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Received on 14-03-2012 *Accepted on 28-03-2012*

Abstract

Simple, fast and precise simultaneous spectrophotometric methods for simultaneous estimation of two-component drug mixture of Telmisartan and Metoprolol Succinate in combined tablet dosage form have been developed. The proposed first method is based on the formation and solving of simultaneous equations using 295.0 and 275.0 nm as two analytical wavelengths. The second method is absorbance ratio method, which uses 282.0 and 295.0 nm as two analytical wavelengths. Third method is based on multicomponent mode method. Developed method was applied to laboratory mixture and its marketed formulation. These methods were statistically validated and recovery studies confirmed the accuracy of the proposed method.

Key Words: Telmisartan, Metoprolol Succinate, Simultaneous equations, Absorbance Ratio and Multicomponent mode method.

Introduction

Telmisartan (TEL) is 2-(4-{[4-methyl-6-(1-methyl-1H-1, 3-benzodiazol-2-yl)-2-propyl-1H-1, 3-benzodiazol-1-yl] methyl} phenyl) benzoic acid (Fig.1) is an non-peptide molecule, angiotensin II receptor (type AT1) antagonist [1,2]. It acts by blocking the vasoconstrictor and aldosterone secreting effect of angiotensin II by selective blocking the binding of angiotensin II to AT1 receptor found in vascular smooth muscles[3]. It is not official in any pharmacopoeia. It is an effective agent for the treatment of hypertension and renal impairment. It has a lower incidence of cough than ACE inhibitors. It is white to off-white crystalline powder that is insoluble in water, freely soluble in methanol and acetonitrile [4].

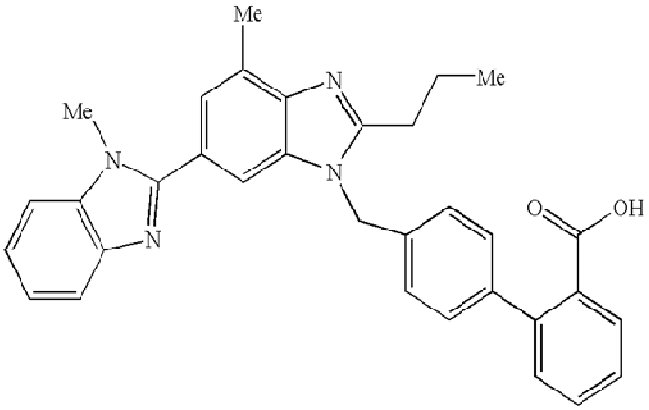

Fig. 1: Structure of Telmisartan (TEL)

Metoprolol Succinate (MPS) is (*RS*)-1-(Isopropylamino)-3-[4-(2-methoxyethyl) phenoxy]propan-2-ol-Butanedioic acid (2:1) (salt) (Fig.2) is a cardio selective drug used in the treatment of hypertension and various cardiovascular disorders. The action of Metoprolol succinate is mediated through the beta1-selective adrenoceptor blockage, thus causing reduction in heart rate and cardiac output. It is a beta1-selective drug which belongs to the chemical class of beta blockers with molecular formula of $(C_{15}H_{25}NO_3)_2$. $C_4H_6O_4$ and molecular weight is 652.81. It's freely soluble in water, soluble in methanol, slightly soluble in alcohol, very slightly soluble in ethyl acetate [5,6]

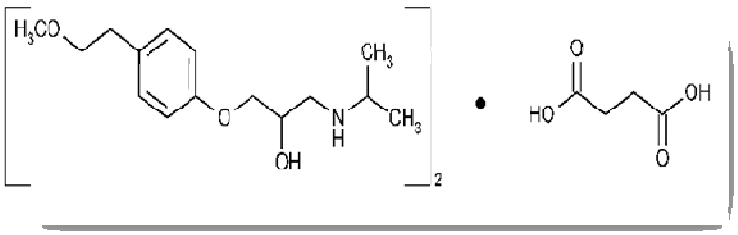

Fig. 2: Structure of Metoprolol Succinate (MPS)

Many methods have been reported in the literature for the estimation of TEL and MPS, individually or in combination with other drugs [7-19]. However, there is no method reported for the simultaneous estimation of TEL and MPS. The multicomponent dosage form includes multiple entities and excipients; and poses considerable challenge to the analytical chemist during the development of assay procedure. The present study

was aimed at the simultaneous estimation of TEL and MPS by simultaneous equation, absorbance ratio and multicomponent mode analysis method. These methods were validated according to the ICH guidelines.

Materials and Methods

Equipment

Shimadzu UV-1700; UV/VIS double beam spectrophotometer with spectral bandwidth of 2 nm, wavelength accuracy ±0.5 nm (with automatic wavelength correction) and wavelength readability 0.1 nm increment was employed for all measurements using a matched pair of 10 mm quartz cells.

Materials

Gift sample of TEL and MPS were procured from Ipca Laboratories Limited Ratlam M.P., India. The commercial fixed dose combination product **TELMAXX 25 tab** label claim (Telmisartan 40mg, Metoprolol Succinate 25mg ER) manufactured manufactured in India by Glenmark Pharmaceuticals Ltd. was procured from the local pharmacy. 0.1 N NaOH used as a solvent.

Preparation of Stock Solutions

For the preparation of standard stock solution about Telmisartan (TEL) 100 mg of and 250 mg of Metoprolol Succinate (MPS) were accurately weighed and transferred to two separate 100 ml volumetric flasks. Each drug was dissolved in 75 ml of 0.1 N NaOH and shaken gently for 10 min. The volume was made up to the mark with 0.1 N NaOH to get stock solution of 1000 µg/ml and 2500 µg/ml respectively. From above solution take 10 ml of the solution in volumetric flask and then diluted up to 100ml with 0.1 N NaOH to produce final stock solution of 100 µg/ml and 250 µg/ml.

Development of Methods

Method 1: Simultaneous equation: From the stock solutions, 1.2 ml of TEL and 6 ml of MPS was transferred to two separate 10 ml volumetric flasks and the volume was adjusted to the mark with 0.1 N NaOH i.e. strength obtained was 10µg/ml for TEL and 150µg/ml for MPS. Both the drug solutions were scanned separately between 200 nm to 400 nm. The overlain spectrum of both drugs was recorded (Shown in Fig.3) and two wavelengths 295.0 nm (λ max of TEL) nm and 275.0 nm (λ max of MPS) were selected for estimation of drugs using simultaneous equation method and construction of calibration curves.

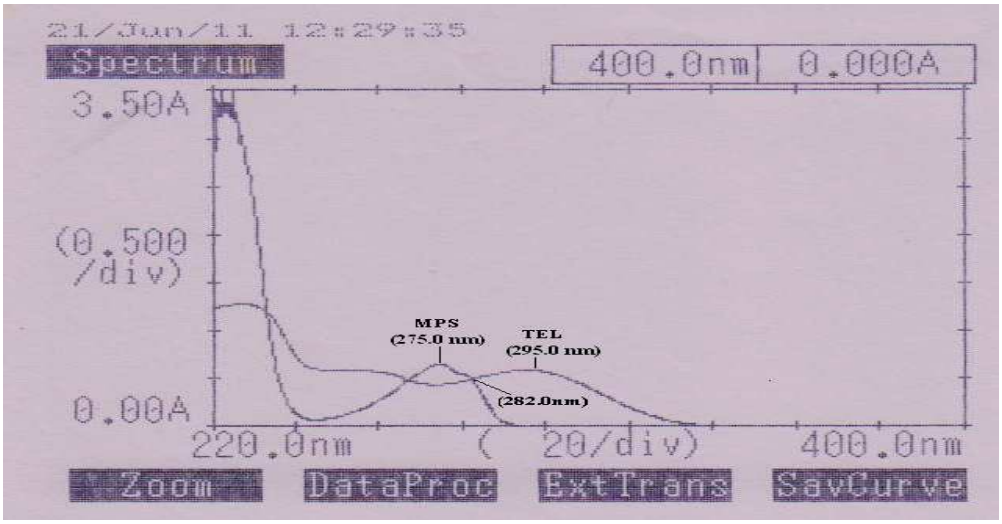

Fig.3: Overlain spectra of TEL and MPS

Two series of different concentration in range of 4-24 µg/ml for TEL and 25-250 µg/ml for MPS were prepared from the working standard solutions. The calibration curves were plotted at 295.0 and 275.0 nm. The absorptivities ($A_{1\%}$, 1 cm) of both the drugs at both the wavelength were determined. These calculated values were the mean of five independent determinations. The absorbance and absorptivity value at the particular wavelength were calculated and substituted in the following equation to obtain the concentrations:

$$C_X = \frac{A_2 \times 0 - A_1 \times 43.46}{-21175.885} \quad \ldots\ldots\ldots\ldots\ldots (1)$$

$$C_Y = \frac{A_1 \times 362.3 - A_2 \times 487.25}{-21175.885} \quad \ldots\ldots\ldots\ldots\ldots (2)$$

where A_1 and A_2 are absorbance of sample solution at 295.0 nm and 275.0 nm respectively C_X and Cy are concentration of TEL and MPS respectively (mole/lit) in sample solution the validity of formed equation was checked by preparing three mixed standards measuring there absorbance at respective wavelength and comparing these with the absorbance calculated using above formed equations.

Method 2: Absorbance Ratio method

From the overlain spectra of TEL and MPS, 295.0 nm was taken as λmax for TEL and 282.0 nm as isoabsorptive point for estimation of MPS. Series of different concentrations in range of 4-24 µg/ml for TEL and 25-250 µg/ml for MPS were prepared from the working standard solutions. The calibration curves were plotted at 282.0 and 295.0 nm. The absorptivities ($A_{1\%}$, 1 cm) of both the drugs at both the wavelength were determined. These calculated values were the mean of five independent determinations. The concentration of sample was measured by this equation,

$$C_{TEL} = Q_M - Q_Y/Q_X - Q_Y \times A_1/a_{x1} \quad \text{---------- (3)}$$

$$C_{MPS} = Q_M - Q_X/Q_X - Q_Y \times A_1/a_{y1} \quad \text{---------- (4)}$$

Method 3: Multicomponent Mode Method: In this method five mixed standards of TEL and MPS in the having concentrations in µg/ml of 4:25, 6:50, 8:100, 10:150 and 12:200 were prepared by appropriate dilution of the standard stock solutions and scanned in the region of 400 nm to 200 nm. Sampling wavelengths (295.0 nm and 275.0 nm) were selected considering the peaks and valleys in the UV spectra of the individual components. The concentration of individual drug was feed to the multi-component mode of the instrument. The instrument collects and compiles the spectral data from mixed standards and the concentration of the various components of the formulation are directly recorded when the sample solution is scanned (Shown in Fig.4). The analysis was repeated for three times.

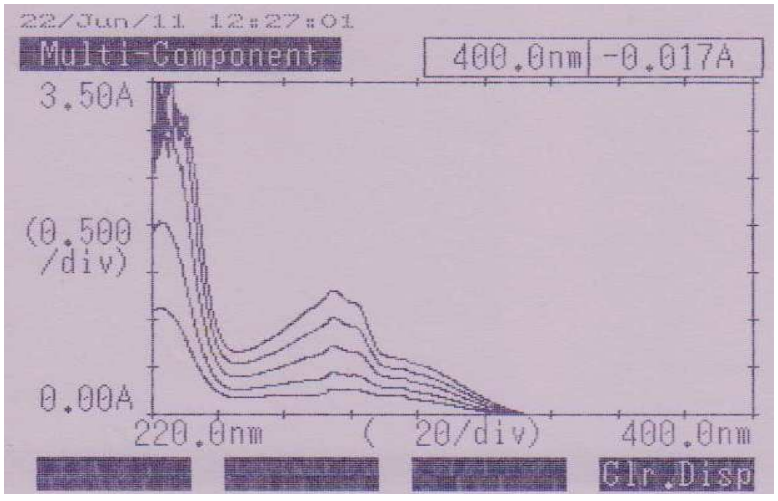

Fig. 4: Overlain Spectra of Mixed Standards

Estimation from formulation:

Twenty tablet were weigh, crushed and mixed thoroughly. Weigh tablet powder equivalent to 40 mg of TEL and 25 mg of MPS was taken in a stoppered volumetric flask (100.0ml); 75ml of 0.1N NaOH was added and sonicated for 5 min. The volume was then made up to the mark using same solvent. The solution was filtered through Whatmann filter paper (No 41). From this stock solution, 0.1 ml of solution was transferred in 10 ml of volumetric flask. As the amount of MPS pretend in the prepared dilution is below linearity range. The solution was spiked and pure drug sample solution of MPS to give 25µg/ml of MPS. The final dilution contains 4 µg/ml of TEL and 25µg/ml of MPS. The concentrations of dilution were given by multi component mode because this concentration within the Beer's law limit (µg/ml)) for both drugs. The absorbances were noted at respective wavelengths. The concentration of each drug in tablet formulation was determined using above methods.

To study the accuracy (percentage recovery), for both developed methods, recovery studies were carried out by the addition of standard drug solution to pre-analyzed tablet sample with proper dilutions at three different concentration levels (80, 100, and 120%) within the range of linearity for both the drugs.

Results and Discussion

The proposed methods developed for simultaneous analysis of TEL and MPS in combined capsule dosage form was found to be simple, accurate, rapid, economical and sensitive to be applied in routine analysis of tablet. In the described methods there were no additional extraction or separation procedures to extract the drug from the formulation excipient matrix. The elimination of these procedures there by reduces the error in quantitation. First method was developed by formation and solving of simultaneous equation based on absorptivity coefficient of two drugs at λmax.

Once the equation is framed, the absorbance of sample solution at selected wavelengths was to be measured followed by simple calculation.

Framed equation was validated using laboratory prepared mixed standards of two drugs which gave satisfactory results.

In second developed method (absorbance ratio method) for estimation TEL and MPS, two wavelengths were selected from overlain spectra. The spectra of TEL and MPS when overlaid indicated that the isoabsorptive point was at 282.0 nm at which estimation of MPS was done and estimation of TEL was done at its λmax 295.0 nm.

By observing the validation parameters (Table 2), methods found to be specific, accurate, precise, repeatable and reproducible. Methods can be employed for routine analysis of tablet for assay. The methods were found to be accurate, precise and rugged.

Table-1: Summary of optical characteristic.

Parameters (Units)	***Telmisartan***			***Metoprolol Succinate***		
	Method **I**	Method **II**	Method **III**	Method **I**	Method **II**	**Method III**
Linearity range (µg/ml)	**4-24**	**4-24**	**4-24**	**25-250**	**25-250**	**25-250**
λmax (nm)	**295.0**	**295.0**	**295.0**	**275.0**	**282.0**	**275.0**
r^2	**0.9996**	**0.9996**	**0.9996**	**0.9998**	**0.9998**	**0.9998**
Slope±SD	**0.0484**	**0.0484**	**0.0484**	**0.0044**	**0.0034**	**0.0044**

Table-2: Summary of analytical method validation.

Parameters (Units)	***Telmisartan***			***Metoprolol Succinate***		
	Method **I**	Method **II**	Method **III**	Method **I**	Method **II**	**Method III**
LOD (µg/ml)	**0.170**	**0.191**	**0.170**	**1.42**	**1.45**	**1.42**
LOQ (µg/ml)	**0.516**	**0.597**	**0.516**	**4.31**	**4.41**	**4.31**
Recovery (%)	**102.38**	**103.35**	**100.45**	**102.37**	**101.09**	**101.12**
Precision (%RSD)						
Repeatability (n=5)	**0.55**	**1.0**	**0.86**	**0.50**	**0.56**	**0.56**
Interday (n=3)	**0.57**	**0.58**	**0.51**	**0.41**	**0.49**	**0.43**
Intraday (n=3)	**1.11**	**0.65**	**0.61**	**0.51**	**0.63**	**0.52**
Ruggedness(%RSD)						
Analyst 1	**0.97**	**0.49**	**0.73**	**0.37**	**0.56**	**0.55**
Analyst 2	**0.96**	**0.73**	**0.73**	**0.76**	**0.77**	**0.57**

Conclusion

Methods were found to be simple, specific, and easy to perform and require short time to analyze the samples. Low limit of quantification and limit of detection makes these methods suitable for use in quality control.

Acknowledgement

The authors are thankful to Ipca Laboratories Limited Ratlam M.P., India for providing the gift samples of TEL and MPS.

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