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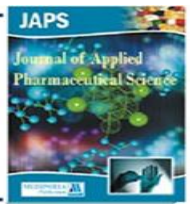

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Development and validation of spectrophotometric method for simultaneous estimation of metoprolol succinate and olmesartan medoxomil in tablet

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ABSTRACT

The present manuscript describes simple, sensitive, rapid, accurate, precise and economic dual wavelength spectrophotometric method for simultaneous determination of metoprolol succinate and olmesartan medoxomil in combined tablet dosage form. The utility of dual wavelength data processing program is its ability to calculate unknown concentration of components of interest in a mixture containing an interfering component. The principle for 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 wavelengths selected for determination of metoprolol succinate were 225.2 nm and 258.2 nm, whereas the wavelengths selected for determination of olmesartan medoxomil were 211 nm and 229.8 nm. The two drugs follow Beer-Lambert's law over the concentration range of 5-30 µg/ml. The method was successfully applied to pharmaceutical dosage form because no interference from the tablet excipients was found. The results of analysis have been validated statistically and by recovery studies.

Key words: Metoprolol succinate, olmesartan medoxomil, dual wavelength spectrophotometric method, validation, tablet.

INTRODUCTION

Metoprolol succinate (METO) is chemically (*RS*)-1-(Isopropylamino)-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol succinate (Maryadele et al., 2006), is a cardio selective β-blocker, used in the treatment of hypertension, angina pectoris, arrhythmia, myocardial infraction and heart failure (Sweetman et al., 2007). It is official in IP, BP and USP. IP (Indian Pharmacopoeia., 2010), BP (British Pharmacopoeia., 2010) and USP (United States Pharmacopoeia., 2005) describe potentiometric method for its estimation. Literature survey reveals UV spectrophotometry (Sawant et al., 2010), RP-HPLC (Vuzic et al., 1995), validated HPLC method for estimation of metoprolol in human plasma (Aqil et al., 2007), spectrophotometric method for simultaneous determination of METO with other drug (Sureshkumar et al., 2010) and RP-HPLC method for simultaneous determination of METO with other drug (Rao et al., 2010) methods for determination of METO in pharmaceutical dosage forms as well as in biological fluids. Olmesartan medoxomil (OLME) is chemically (5-methyl-2-oxo-2*H*-1,3-dioxol-4-yl)methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-({4-[2-(2*H*-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)-1*H*-imidazole-5-carboxylate (Maryadele et al., 2006), is a angiotensin II receptor antagonist for the treatment of hypertension (Sweetman et al., 2007). Olmesartan medoxomil is not official in any pharmacopoeia. Literature survey reveals HPTLC (Parambi et al., 2010), spectrophotometric and HPLC method for simultaneous estimation of OLME with other drug (Wankhede et al., 2009),

HPTLC method for simultaneous estimation of OLME with other drug (Shah et al., 2007), RP-HPLC method for simultaneous estimation of OLME with other drug (Patil et al., 2011), stability-indicating LC (Rane et al., 2009) methods for the determination of OLME in pharmaceutical dosage forms as well as in biological fluids. The combined dosage forms of METO and OLME are available in the market for the treatment of hypertension. The literature survey does not reveal any simple spectrophotometric method for the simultaneous estimation of METO and OLME in their combined dosage form. The present manuscript describes simple, sensitive, accurate, precise, rapid and economic dual wavelength spectrophotometric method for simultaneous estimation of METO and OLME in tablet dosage form.

MATERIALS AND METHODS

Apparatus

A shimadzu model 1600 (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 automatically obtained by UV-Probe system software (UV Probe version 2.10). A Sartorius CP224S analytical balance (Gottingen, Germany), an ultrasonic bath (Frontline FS 4, Mumbai, India) was used in the study.

Reagents and Materials

METO and OLME bulk powder was kindly gifted by Astron Research Centre, Ahmedabad, India. The commercial fixed dose combination product was procured from the local market. Methanol AR grade was procured from S. D. Fine Chemicals Ltd., Mumbai, India.

Preparation of standard stock solutions

An accurately weighed quantity of METO (10 mg) and OLME (10 mg) were transferred to a separate 100 ml volumetric flask and dissolved and diluted to the mark with methanol to obtain standard solution having concentration of METO (100 µg/ml) and OLME (100 µg/ml).

Development of the methods

The solution of METO and OLME were prepared separately in methanol having concentration of 10 µg/ml. They were scanned in the wavelength range of 200 - 400 nm. From the overlain spectra of both drugs, four wavelengths 225.2 nm, 258.2 nm, 211 nm and 229.8 nm were selected for quantitation of both the drugs by proposed dual wavelength spectrophotometric method. The quantitative determination of METO is carried out by measuring the absorbance value at 225.2 nm and 258.2 nm, and the difference between 225.2 nm and 258.2 nm is directly proportional to concentration of OLME in the mixture, whereas determination of OLME is carried out by measuring the absorbance value at 211 nm and 229.8 nm and the difference between 211 nm and 229.8 nm is directly proportional to concentration of METO in the mixture.

Validation of the proposed method

Linearity (Calibration curve)

Appropriate aliquots from the stock solutions of METO and OLME were used to prepare three different sets of dilutions: Series A, B, and C as follows. Series A consisted of different concentration of METO (5-30 µg/ml). Aliquot from the stock solution of METO (100 µg/ml) was pipette out in to a series of 10 ml volumetric flask and diluted with methanol to get final concentration in range of 5-30 µg/ml. Series B consisted of varying concentrations of OLME (5-30 µg/ml). Appropriate volume of the stock solution of OLME (100 µg/ml) was transferred into a series of 10 ml volumetric flask and the volume was adjusted to the mark with methanol. Series C comprised of mixture of METO and OLME having varying concentration of METO and OLME (5-30 µg/ml). The solutions of METO and OLME were prepared by transferring 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 ml equivalent to 5, 10, 15, 20, 25 and 30 µg/ml from the stock solution of METO and OLME (100 µg/ml) into a series of 10 ml volumetric flasks and the volume was adjusted up to the mark with methanol. The absorbance of the solutions of series A, B and C were measured at 211 (λ1), 229.8 (λ2), 225.2 (λ3), and 258.2 nm (λ4). The difference in absorbance between 225.2 nm and 258.2 nm is due to the METO and was plotted against METO concentration (µg/ml). The difference in absorbance between 211 nm and 229.8 nm is due to the OLME and was plotted against OLME concentration (µg/ml) and two different regression equations were obtained.

Method precision (repeatability)

The precision of the instrument was checked by repeated scanning and measurement of the absorbances of solutions (n=6) of METO and OLME (10 µg/ml for both drugs) without changing the parameters.

Intermediate precision (reproducibility)

The intraday and interday precisions of the proposed method was determined by estimating the corresponding responses 3 times on the same day and on 3 different days over a period of one week for 3 different concentrations of standard solutions of METO and OLME (5, 10 and 15 µg/ml). The results were reported in terms of relative standard deviation (% RSD).

Accuracy (recovery study)

The accuracy of the method was determined by calculating the recoveries of METO and OLME by the standard addition method. Known amounts of standard solutions of METO and OLME were at added at 50, 100 and 150 % level to prequantified sample solutions of METO and OLME (5 µg/ml for both drug). The amounts of METO and OLME were estimated by applying obtained values to the respective regression line equations.

Limit of detection and Limit of quantification

The limit of detection (LOD) and the limit of quantification (LOQ) of the drug were derived by calculating the signal-to-noise ratio (S/N, i.e., 3.3 for LOD and 10 for LOQ) using

the following equations designated by International Conference on Harmonization (ICH) guidelines.

$$LOD = 3.3 \times \sigma/S$$
$$LOQ = 10 \times \sigma/S$$

Where, σ = the standard deviation of the response and S = slope of the calibration curve.

Analysis of METO and OLME in combined tablet dosage form

Twenty tablets were weighed and the average weight was calculated. The tablet powder equivalent to 10 mg of METO and 10 mg of OLME were accurately weighed and transferred to 100 ml volumetric flask. Methanol (50 ml) was added and sonicated for 20 min. The volume is adjusted up to the mark with methanol. The solution was then filtered through Whatman filter paper no. 41. The solution was suitably diluted with methanol to get a final concentration of 10 µg/ml of METO and 10 µg/ml of OLME. The absorbances of final solution were recorded at selected wavelengths for determination of OLME and METO. The analysis procedure was repeated three times with tablet formulation.

RESULTS AND DISCUSSION

The solution of METO and OLME were prepared separately in methanol and scanned in the UV range of 200 - 400 nm. From the overlain spectra of both drugs, four wavelengths 225.2 nm, 258.2 nm, 211 nm and 229.8 nm were selected for quantitation of both the drugs by proposed dual wavelength spectrophotometric method (Figure 1).

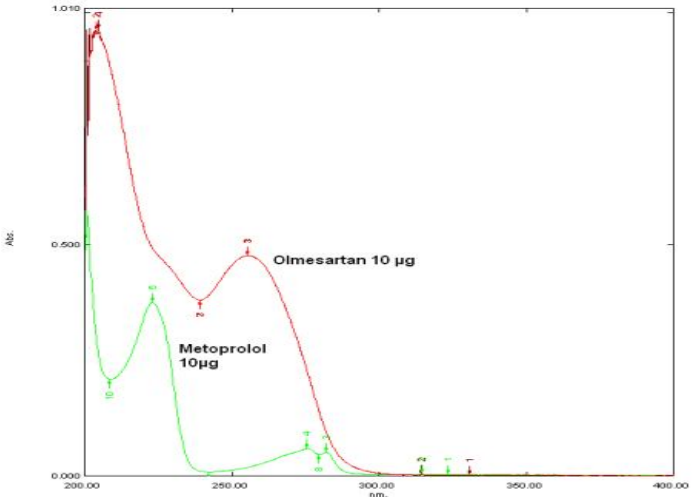

Fig. 1: Overlain absorption spectra of METO and OLME in methanol.

In this method, four specific wavelengths were selected, first wavelength λ1 and second wavelength λ2 at which METO have same absorbances. These two selected wavelengths were employed to determine the concentration of OLME from the mixture of OLME and METO. The difference in absorbance at these two wavelengths (A_{211}– $A_{229.8}$) cancels out the contribution of absorbance of METO in mixture. Third wavelength λ3 and fourth wavelength λ4 at which OLME have same absorbances. These two selected wavelengths were employed to determine the concentration of METO from the mixture of OLME and METO. The difference in absorbance at these two wavelengths ($A_{225.2}$– $A_{258.2}$) cancels out the contribution of absorbance of OLME in mixture.

The proposed method was found to be simple, sensitive, rapid, accurate, precise and economic for the routine simultaneous estimation of two drugs. The linearity ranges for both drugs were found to be 5-30 µg/ml. Precision was calculated as repeatability (relative standard deviation) and intra and inter day variation (% RSD) for both the drugs. Accuracy was determined by calculating the recovery, and the mean was determined (Table 1). The LOD and LOQ were found to be 0.86 and 2.85 µg/ml, respectively for METO and 1.11 and 3.65 µg/ml, respectively for OLME indicates sensitivity of the proposed method. The method was successfully used to determine the amounts of METO and OLME present in tablets (Table 2). Regression analysis data and summary of all the validation parameters for method is given in Table 3.

Table 1: Recovery data of proposed method.

Drug	Level	Amount taken (µg/ml)	Amount added (µg/ml)	Amount found (µg/ml)	% Recovery ± S. D. (n = 3)
OLME	I	5	2.5	7.42	98.97 ± 1.28
	II	5	5	9.98	99.80 ± 1.50
	III	5	7.5	12.54	100.3 ± 0.77
METO	I	5	2.5	7.50	99.97 ± 0.43
	II	5	5	9.82	98.21 ± 0.58
	III	5	7.5	12.65	101.2 ± 1.16

Table 2: Analysis of OLME and METO by proposed method .

Tablet	Label claim (mg)		Amount found (mg)		% Label claim ± S. D. (n=3)	
	METO	OLME	METO	OLME)	METO	OLME
I	200	200	200.8	199	100.4	99.50
II	200	200	201.4	198.6	100.7	99.30

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

Parameters	METO	OLME
Wavelength (nm)	225.2, 258.2 nm	211, 229.8 nm
Beer's Law Limit (µg/ml)	5 - 30	5 - 30
Regression equation (y = a + bc)	y = 0.0316x-	y = 0.0453x-
Slope (b)	0.0218	0.0653
Intercept (a)	0.0316	0.0453
	-0.0218	-0.0653
Correlation Coefficient (r^2)	0.9991	0.9996
Sandell's sensitivity (mcg/cm^2/0.001 AU)	0.0333	0.0254
Molar extinction co-efficient (L mol^{-1} cm^{-1}/ M^{-1} cm^{-1})	19067.6	20611.8
Accuracy (% Recovery) (n = 3)	99.69 ± 1.18	99.79 ± 0.72
Repeatability (% RSD[a], n = 6)	0.46	0.57
Interday (n = 3) (% RSD)	0.34-0.67	0.48-0.73
Intraday(n = 3) (% RSD)	0.35-1.07	0.52-1.22
LOD[b] (µg/ml)	0.86	1.11
LOQ[c] (µg/ml)	2.85	3.65

[a]RSD = Relative standard deviation. [b]LOD = Limit of detection. [c]LOQ = Limit of quantification

CONCLUSION

The results of the analysis of pharmaceutical tablet formulation by the proposed method are highly reproducible and

reliable and are in good agreement with the label claim of the drug. The additives usually present in the pharmaceutical formulations of the assayed samples did not interfere with determination of deflazacort. The observations and results obtained from this study including linearity, accuracy and precision (method precision as repeatability and intermediate precision as intra and inter day precision) are lie well within acceptable results. From the experimental studies it can be concluded that proposed method is sensitive, accurate and precise and can be adopted for the routine analysis of both drugs in tablet without interference of excipients.

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