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Development and Validation of Spectrophotometric Method for Simultaneous Determination of Metoprolol Succinate and Olmesartan Medoxomil in Tablet Dosage Form

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Abstract

The present manuscript describe simple, sensitive, rapid, accurate, precise and economical spectrophotometric method based on simultaneous equation method for the simultaneous determination of metoprolol succinate and olmesartan medoxomil in combined tablet dosage form. The method is based on the simultaneous equations for analysis of both the drugs using methanol as solvent. Metoprolol succinate has absorbance maxima at 223 nm and olmesartan medoxomil has absorbance maxima at 255 nm in methanol. The linearity was obtained in the concentration range of 5-30 µg/ml for both metoprolol succinate and olmesartan medoxomil. The concentrations of the drugs were determined by using simultaneous equations method. The mean recovery was 99.63 ± 0.47 and 100.8 ± 1.36 for metoprolol succinate and olmesartan medoxomil respectively. The method was found to be simple, sensitive, accurate and precise and was applicable for the simultaneous determination of metoprolol succinate and olmesartan medoxomil in pharmaceutical tablet dosage form. The results of analysis have been validated statistically and by recovery studies.

Keywords: Recovery, Simultaneous equations, Validation.
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Introduction

Metoprolol succinate (METO) is chemically (*RS*)-1-(Isopropylamino)-3-[4-(2-methoxyethyl) Phenoxy]propan-2-ol succinate [1], is a cardio selective β-blocker, used in the treatment of hypertension, angina pectoris, arrhythmia, myocardial infraction and heart failure[2]. It is official in Indian Pharmacopoeia (IP), British Pharmacopoeia (BP) and United States Pharmacopoeia (USP). IP[3], BP[4] and USP[5] describe potentiometric method for its estimation. Various methods like UV spectrophotometry[6], RP-HPLC[7], validated HPLC method for estimation of metoprolol in human plasma[8], spectrophotometric method for simultaneous determination of METO with other drug[9] and RP-HPLC method for simultaneous determination of METO with other drug[10] are reported in literature for estimation 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[11], is a angiotensin II receptor antagonist for the treatment of hypertension[12]. Olmesartan medoxomil is not official in any pharmacopoeia. Various methods like HPTLC[13], spectrophotometric and HPLC method for simultaneous estimation of OLME with other drug[14], HPTLC method for simultaneous

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estimation of OLME with other drug[15], RP-HPLC method for simultaneous estimation of OLME with other drug[16] and stability-indicating LC method[17] for the determination of OLME are reported in literature for estimation 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. Literature survey does not reveal any simple spectroscopic method for determination of METO and OLME in combined dosage form. The present manuscript describes simple, sensitive, accurate, precise, rapid and economic spectrophotometric method based on simultaneous equations for simultaneous estimation of METO and OLME in tablet dosage form.

Materials and Methods

Apparatus

A shimadzu model 1700 (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, Gujarat, India. The commercial fixed dose combination product was procured from the local market. Methanol (AR Grade, Finar Chemicals Ltd., Ahmedabad, India) and Whatman filter paper no. 41 (Millipore, USA) were used in the study.

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).

Method

The standard solutions of METO (20 µg/ml) and OLME (20 µg/ml) were scanned separately in the UV range of 200-400 nm to determine the λ_{max} of both the drugs. The λ_{max} of METO and OLME were found to be 223 nm and 255.4 nm respectively. Six standard solutions having concentration 5, 10, 15, 20, 25 and 30 µg/ml for METO and OLME were prepared in methanol using the standards solutions. The absorbance of resulting solutions was measured at 223 nm and 255.4 nm and calibration curves were plotted at these wavelengths. The absorptivity coefficients of these two drugs were determined using calibration curve equations. The concentration of METO and OLME in sample solution was determined by solving the respective simultaneous equations[18] generated by using absorptivity coefficients and absorbance values of METO and OLME at these wavelengths.

Validation of the proposed method

The proposed method was validated according to the International Conference on Harmonization (ICH) guidelines[18].

Linearity (Calibration curve)

The calibration curves were plotted over a concentration range of 5-30 µg/ml for both METO and OLME. Accurately measured standard solutions of METO (0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 ml) and OLME (0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 ml) were transferred to a series of 10 ml of volumetric flasks and diluted to the mark with methanol. The absorbances of the solutions were measured at 223 and 255.4 nm against methanol as blank. The calibration curves were constructed by plotting

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absorbances versus concentrations and the regression equations were calculated.

Method precision (repeatability)

The precision of the instrument was checked by repeated scanning and measurement of absorbance of solutions (n = 6) for METO and OLME (10 µg/ml for both METO and OLME) without changing the parameter of the proposed spectrophotometry method.

Intermediate precision (reproducibility)

The intraday and interday precision of the proposed method was determined by analyzing the corresponding responses 3 times on the same day and on 3 different days 3 different concentrations of standard solutions of METO and OLME (10, 20, 30 µg/ml for both METO and OLME).

Accuracy (recovery study)

The accuracy of the method was determined by calculating recovery of METO and OLME by the standard addition method. Known amounts of standard solutions of METO and OLME were added at 50, 100 and 150 % level to prequantified sample solutions of METO and OLME (10 µg/ml for both drug). The amounts of METO and OLME were estimated by applying obtained values to the respective regression line equations. The experiment was repeated for five times.

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) 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 powdered. The powder equivalent to 10 mg of METO and 10 mg of OLME was transferred to a 100 ml volumetric flask. Methanol (50 ml) was added to it and sonicated for 20 min. The solution was filtered through Whatman filter paper No. 41 and the volume was adjusted up to the mark with methanol. The above 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 the tablet sample solution i.e. A_1 and A_2 were recorded at 223 nm and 255.4 nm and ratios of absorbance were calculated, i.e. A_2/A_1. Relative concentration of two drugs in the sample solution was calculated using respective simultaneous equations generated by using absorptivity coefficients and absorbance values of METO and OLME at these wavelengths.

Results and Discussion

In this method, two wavelengths were used for the analysis of the drugs. 223 nm (λmax of METO and 255.4 nm (λmax of OLME) are the wavelengths at which calibration curves were prepared for both the drugs. The criteria for obtaining maximum precision [19] by this method were calculated and found to be out side the range 0.1-2. Once the absorptivity values are determined very little time is required for analysis, as would require determination of absorbances of the sample solution at two selected wavelengths and few simple calculations.

The standard solutions of METO and OLME were scanned separately in the UV range, and zero-order spectra for METO (Figure 1) and OLME (Figure 2) were recorded. Maximum absorbance was obtained at 223 nm and 255.4 nm for METO and OLME respectively. These two wavelengths were employed for the determination of METO

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and OLME without any interference from the other drug in their combined formulations.

Linear correlation was obtained between absorbances and concentrations of METO and OLME in the concentration ranges of 5-30 µg/ml for both drugs. The linearity of the calibration curve was validated by the high values of correlation coefficient of regression. The RSD values of METO were found to be 0.46 % and 0.33 % at 223 and 255.4 nm, respectively. The RSD value of OLME was found to be 0.57 % and 0.40 % at 223 and 255.4 nm respectively. Relative standard deviation was less than 2 %, which indicates that proposed method is repeatable. The low RSD values of interday (0.42-0.50 % and 0.28-0.39 % for METO at 223 and 255.4 nm respectively and 0.52-0.63 % and 0.35-0.47 % for OLME at 223 and 255.4 nm respectively) and intraday (0.11-0.68 % and 0.21-0.53 % for METO at 223 and 255.4 nm respectively and 0.21-0.51 % and 0.17-0.60 %for OLME at 223 and 255.4 nm respectively) variation for METO and OLME reveal that the proposed method is precise. LOD and LOQ values for METO were found to be 0.98 and 0.85 µg/ml and 3.25 and 2.81 µg/ml at 223 and 255.4 nm respectively. LOD and LOQ values for OLME were found to be 0.92 and 1.03 µg/ml and 3.04 and 3.40 µg/ml at 223 and 255.4 nm respectively. These data show that method is sensitive for the determination of METO and OLME. All the regression analysis data and summary of validation parameters for the proposed method is reported in Table 1.

The recovery experiment was performed by the standard addition method. The mean recoveries were 99.63 ± 0.47 and 100.8 ± 1.36 for METO and OLME respectively indicates accuracy of the proposed method (Table 2). The proposed validated method was successfully applied to determine METO and OLME in their combined dosage form. The results obtained for METO and OLME were comparable with the corresponding labeled amounts (Table 3). No interference of the excipients with the absorbance of interest appeared; hence the proposed method is applicable for the routine simultaneous estimation of METO and OLME in pharmaceutical tablet dosage forms

Conclusion

The proposed spectrophotometric method was found to be simple, sensitive, accurate and precise for simultaneous determination of METO and OLME in tablet dosage form. The method utilizes easily available and low cost solvent like methanol for analysis of METO and OLME hence the method was also found to be economic for estimation of METO and OLME from tablet. The method has linear response in the range of 5-30 µg/ml for both METO and OLME in methanol. The result of the analysis of pharmaceutical formulation by the proposed method is highly reproducible and reliable and it is in good agreement with the label claim of the drug. The additives usually present in the pharmaceutical formulation of the assayed sample did not interfere with determination of METO and OLME. The method can be used for the routine analysis of the METO and OLME in combined dosage form without any interference of excipients.

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TABLE 1: REGRESSION ANALYSIS DATA AND SUMMARY OF VALIDATION PARAMETERS FOR THE PROPOSED METHOD

Parameters	METO		OLME	
Wavelength (nm)	223	255.4	223	255.4
Beer's law limit (µg /ml)	5-30	5-30	5-30	5-30
Sandell's sensitivity (µg/cm^2/0.001 Absorbance Unit)	0.0270	0.7092	0.0212	0.0215
Regression equation (y = a + bc)	y = 0.0363x-	y = 0.0009x-	y= 0.0505x-	y= 0.0463x-
Slope (b)	0.0079	0.0024	0.0456	0.0367
Intercept (a)	0.0363	0.0009	0.0505	0.0463
	0.0079	0.0024	0.0456	0.0367
Correlation coefficient (r^2)	0.9999	0.9991	0.9996	0.9990
LOD (µg/ml)	0.98	0.85	0.92	1.03
LOQ (µg /ml)	3.25	2.81	3.04	3.40
Repeatability (% RSD, n = 6)	0.46	0.33	0.57	0.40
Precision (% RSD, n = 3)				
Interday	0.42-0.50	0.28-0.39	0.52-0.63	0.35-0.47
Intraday	0.11-0.68	0.21-0.53	0.21-0.51	0.17-0.60
Accuracy (% recovery, n = 5)	99.63 ± 0.47		100.8 ± 1.36	

TABLE 2: RECOVERY DATA OF PROPOSED METHOD

Drug	Amount taken (µg/ml)	Amount added (%)	% Recovery ± S. D. (n = 5)
METO	5	50	99.47 ± 0.28
	5	100	98.28 ± 0.41
	5	150	101.1 ± 0.73
OLME	5	50	101.8 ± 1.84
	5	100	99.82 ± 0.53
	5	150	100.8 ± 1.62

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

TABLE 3: ANALYSIS OF METO AND OLME BY PROPOSED METHOD

Tablet Brand	Label claim (mg)		Amount found (mg)		% Label claim ± S. D. (n = 6)	
	METO	OLME	METO	OLME)	METO	OLME
I	10	10	10.04	9.91	100.4 ± 0.87	99.12 ± 0.65
II	10	10	9.97	9.87	99.73 ± 1.12	98.73 ± 1.37

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

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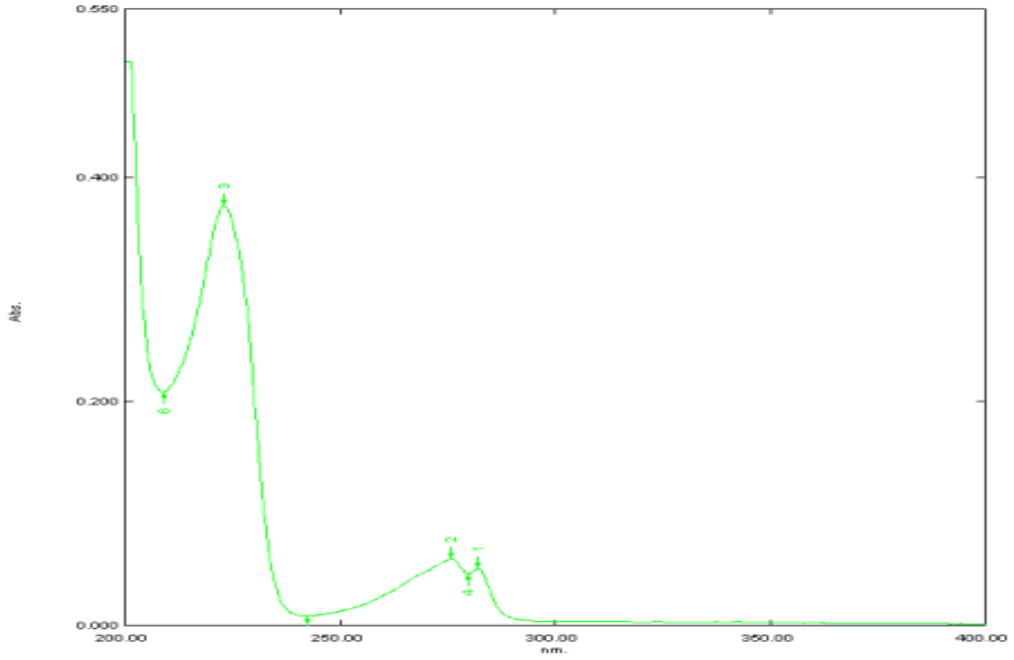

FIG. 1. ZERO-ORDER ABSORPTION SPECTRA OF METO IN METHANOL

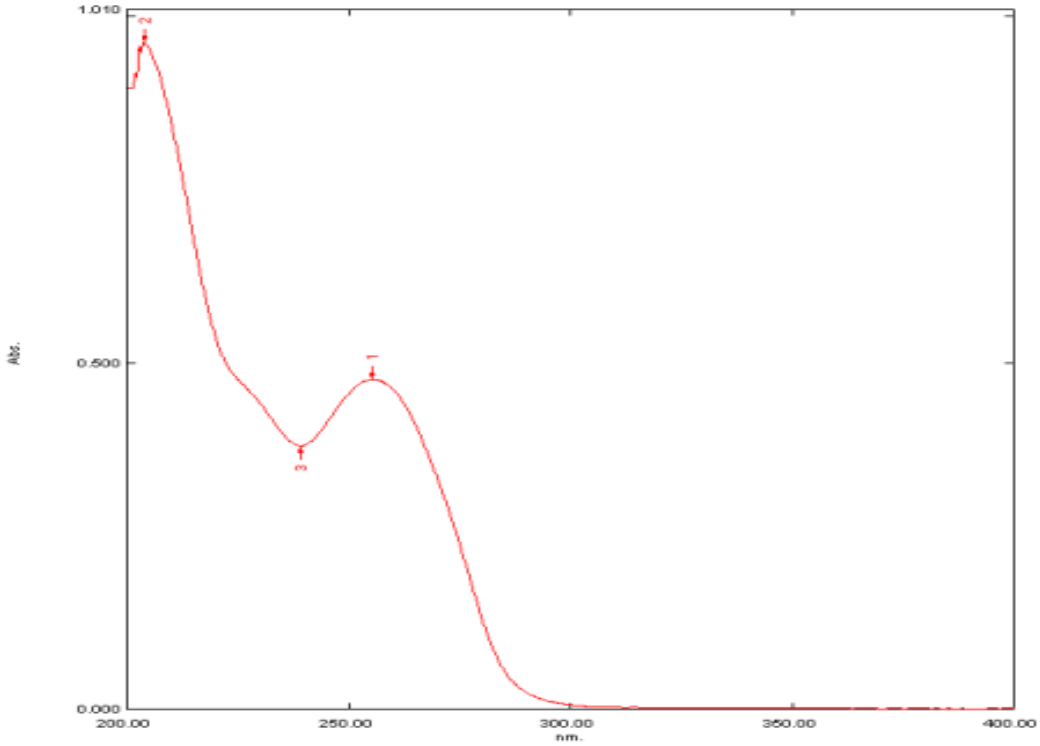

FIG. 2. ZERO-ORDER ABSORPTION SPECTRA OF OLME IN METHANOL

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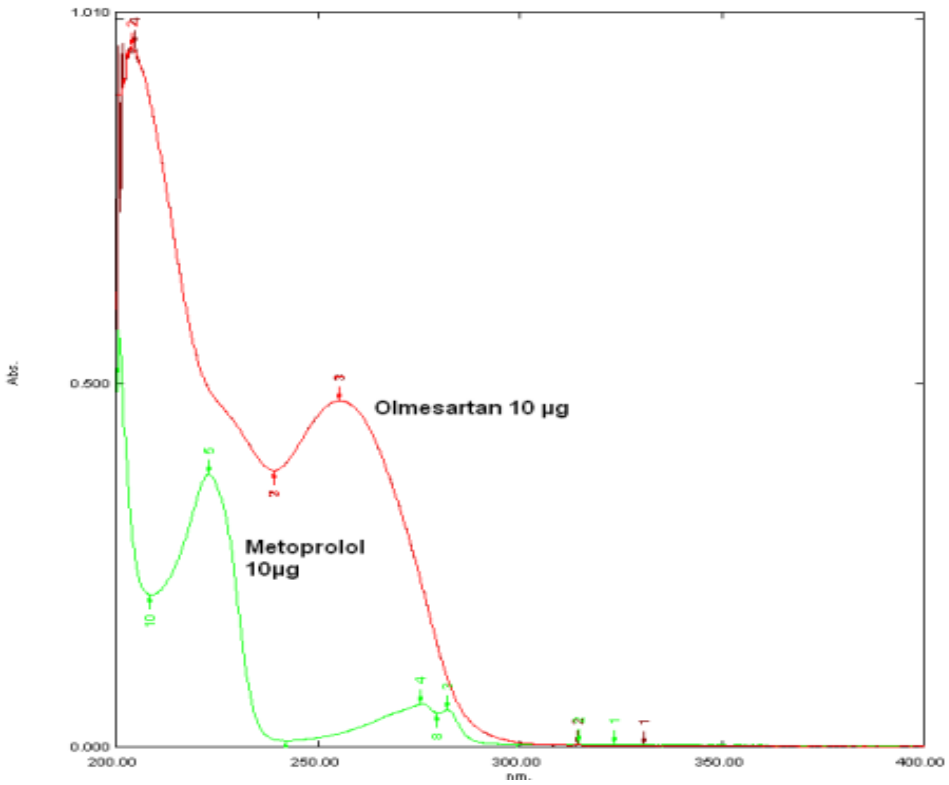

FIG. 3. OVERLAIN ZERO-ORDER ABSORPTION SPECTRA OF METO AND OLME IN METHANOL

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