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Development and Validation of First Order Derivative Spectrophotometric method for simultaneous estimation of Metoprolol Succinate and Olmesartan Medoxomil in tablets

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ABSTRACT:

The present manuscript describe simple, sensitive, rapid, accurate, precise and economical first derivative spectrophotometric method for the simultaneous determination of metoprolol succinate and olmesartan medoxomil in combined tablet dosage form. The derivative spectrophotometric method was based on the determination of both the drugs at their respective zero crossing point (ZCP). The first order derivative spectra was obtained in methanol and the determinations were made at 204.6 nm (ZCP of olmesartan medoxomil) for metoprolol succinate and 275.6 nm (ZCP of metoprolol succinate) for olmesartan medoxomil. The linearity was obtained in the concentration range of 5-30 µg/ml for metoprolol succinate and 5-30 µg/ml for olmesartan medoxomil. The mean recovery was 99.80 ± 1.50 and 99.90 ± 0.36 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: Metoprolol succinate, Olmesartan medoxomil, First order derivative spectrophotometric method, Tablet, 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 IP [3], BP [4] and USP [5]. IP [3], BP [4] and USP [5] describe potentiometry method for its estimation. Literature survey reveals UV spectrophotometric method [6], RP-HPLC method [7], validated HPLC method for estimation of metoprolol in human plasma [8], simultaneous spectrophotometric method with other drug [9] and RP-HPLC method with other drug [10] 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.Literature survey reveals stress induced method UV spectrometric method[13], HPTLC[14], simultaneous estimation with other drug[15], HPTLC with other drug[16], RP-HPLC with other drug[17], stability-indicating LC method[18] for the determination of OLME. The combined dosage forms of METO and OLME are available in the market for the treatment of hypertension. The present manuscript describes simple, sensitive, accurate, precise, rapid and economic spectrophotometric method based on simultaneous equations for simultaneous estimation of metoprolol succinate and olmesartan medoxomil in tablet dosage form.

MATERIALS AND METHODS

Apparatus

A double beam UV/Visible spectrophotometer (Shimadzu model 1700, Japan) 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. An analytical balance (Sartorius CP224S, 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. Finar Chemicals Ltd., Ahmedabad, 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).

Methodology

The standard solutions of METO (10 µg/ml) and OLME (10 µg/ml) were scanned separately in the UV range of 200-400 nm. The zero-order spectra thus obtained was then processed to obtain first-derivative spectra. Data were recorded at an interval of 1 nm. The two spectra were overlain and it appeared that METO showed zero crossing at 275.6 nm, while OLME showed zero crossing at 204.6 nm. At the zero crossing point (ZCP) of METO (275.6 nm), OLME showed a first-derivative absorbance, whereas at the ZCP of OLME (204.6 nm), METO showed a first-derivative absorbance. Hence 204.6 and 275.6 nm was selected as analytical wavelengths for determination of METO and OLME, respectively. These two wavelengths can be employed for the determination of METO and OLME without any interference from the other drug in their combined dosage formulations.

Validation of the proposed method

The proposed method was validated according to the International Conference on Harmonization (ICH) guidelines[19].

Linearity (Calibration curve)

The calibration curves were plotted over a concentration range of 5-30 µg/ml for METO and 5-30 µg/ml for 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. First-derivative absorbance (D1) was measured at 204.6 nm for METO and 275.6 nm for OLME. The calibration curves were constructed by plotting 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 solution (n = 6) for METO and OLME (10 µg/ml) without changing the parameter of the first-derivative 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 over a period of 1 week for 3 different concentrations of standard solutions of METO and OLME (5, 10 and 15 µg/ml). The result was reported in terms of relative standard deviation (% RSD).

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 (5 µg/ml for each 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, i.e., 3.3 for LOD and 10 for LOQ) using the following equations designated by International Conference on Harmonization (ICH) guidelines[19].

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

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

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. This solution is expected to contain 100 µg/ml of METO and 100 µg/ml of OLME. This solution (1.0 ml) was taken in to a 10 ml volumetric flask and the volume was adjusted up to mark with methanol to get a final concentration of METO (10 µg/ml) and OLME (10 µg/ml). The responses of the sample solution were

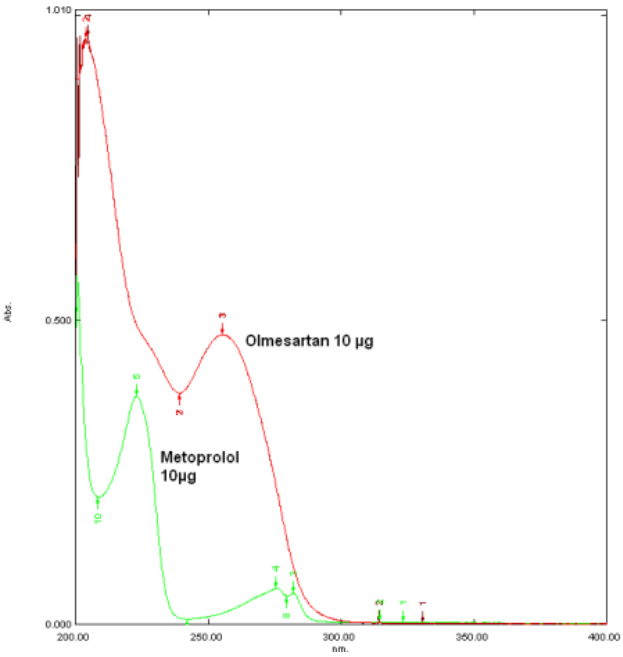

Figure 1: Overlain zero-order absorption spectra of METO and OLME in methanol

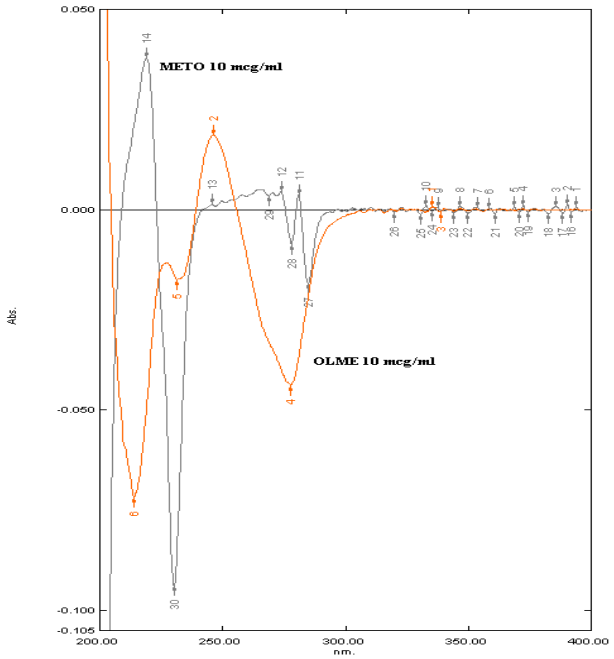

Figure 2: Overlain first-order derivative spectra of METO and OLME in methanol

measured at 204.6 nm and275.6 nm for quantification of METO and OLME, respectively. The amounts of the METO and OLME present in the sample solution were calculated by fitting the responses into the regression equation for METO and OLME in the proposed method.

RESULTS AND DISCUSSION

The standard solutions of METO and OLME were scanned separately in the UV range, and zero-order spectra (Figure 1) thus obtained was then processed to obtain first-derivative spectra. Data were recorded at an interval of 1 nm. The two derivative spectra showed maximum absorbance at 204.6 nm (ZCP of OLME) for METO and 275.6 nm (ZCP of METO) for OLME. First-derivative absorbances (D1) were recorded 204.6 nm for METO and 275.6 nm for OLME (Figure 2). First derivative spectra give good quantitative determination of both the drugs at their respective without any interference from the other drug in their combined dosage formulations. Second and third-ordered derivative spectra of the drugs were not tested because the first-order spectra give satisfactory ZCPs and good quantitative determination of both the drugs without any interference.

Linear correlation was obtained between absorbances and concentrations of METO and OLME in the concentration ranges of 5-30 µg/ml and 5-30 µg/ml, respectively. The linearity of the calibration curve was validated by the high values of correlation coefficient of regression (Table 1). The RSD values for METO and OLME were found to be 0.46 and 0.57 %, respectively (Table 1). The low values of relative standard deviation (less than 2 %) indicate that the proposed method is repeatable. The low RSD values of interday (0.34-0.67 and 0.48-0.73 %) and intraday (0.35-1.07 and0.52-1.22 %)

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

PARAMETERS		First-derivative UV Spectrophotometry	
		METO at 204.6 nm	OLME at 275.6 nm
Concentration range (µg/ml)		5-30	5-30
Regression equation (y = a + bc) Slope (b) Intercept (a)		(y = 0.005x-0.0017) 0.005 -0.0017	(y = 0.004x-0.001) 0.004 -0.001
Correlation Coefficient (r^2)		0.9990	0.9990
Sandell's sensitivity (µg/cm^2/0.001 A.U.)		0.0333	0.0254
Accuracy (% recovery) (n = 5)	Level I	99.80 ± 1.50	99.90 ± 0.36
	Level II	100.5± 1.39	99.71 ± 1.79
	Level III	100.4 ± 1.62	99.98 ± 1.45
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)		0.140 µg/ml	0.164 µg/ml
LOQ[c] (µg/ml)		0.424 µg/ml	0.498 µg/ml

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

Table 2: Recovery data of proposed method

Drug	Level	Amount taken (µg/ml)	Amount added (µg/ml)	Amount found (µg/ml)	% Mean recovery ± S.D. (n = 5)
METO	I	10	5	14.86	99.51 ± 0.75
	II	10	10	20.10	100.5 ± 1.39
	III	10	15	25.10	100.4 ± 1.62
OLME	I	10	5	14.91	99.42 ± 0.91
	II	10	10	19.94	99.71 ± 1.79
	III	10	15	24.99	99.98 ± 1.45

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

for METO and OLME, respectively, reveal that the proposed method is precise (Table 1). LOD values for METO and OLME were found to be 0.140 and 0.164 µg/ml, respectively and LOQ values for METO and OLME were found to be 0.424 and 0.498 µg/ml, respectively (Table 1). These data show that proposed method is sensitive for the determination of METO and OLME.

The recovery experiment was performed by the standard addition method. The mean recoveries were 99.80 ± 1.50 and 99.90 ± 0.36 % for METO and OLME, respectively (Table 2). The results of recovery studies indicate that the proposed method is accurate. 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 dosage forms.

CONCLUSION

Based on the results, obtained from the analysis of described method, it can be concluded that the method has linear response in the range of 5-30 µg/ml and 5-30 µg/ml for METO and OLME, respectively with co-efficient of correlation, (r^2)=0.9990 and (r^2) = 0.9990 for METO and OLME, respectively. 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.

Table 3: Analysis of olme and meto by proposed method

Tablet	Label claim (mg)		Amount found (mg)		% Label claim ± S. D. (n = 6)	
	METO	OLME	METO	OLME)	METO	OLME
I	10	10	9.96	9.93	99.64 ± 0.46	99.33 ± 0.59
II	10	10	9.97	9.96	99.73 ± 0.72	99.65 ± 0.63

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

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