Original Article

Absorbance correction method for estimation of telmisartan and metoprolol succinate in combined tablet dosage forms

Abstract

Aim and Background: The present manuscript describes simple, sensitive, rapid, accurate, precise and economical spectrophotometric method for the simultaneous determination of telmisartan and metoprolol succinate in combined tablet dosage form. **Materials and Methods:** The method is based on the absorbance correction equations for analysis of both the drugs using methanol as solvent. Telmisartan has absorbance maxima at 296 nm and metoprolol succinate has absorbance maxima at 223 nm in methanol. The linearity was obtained in the concentration range of 2-16 μg/ ml and 3-24 μg/ml for telmisartan and metoprolol succinate, respectively. The concentrations of the drugs were determined by using absorbance correction method at both the wavelengths. The method was successfully applied to pharmaceutical dosage form because no interference from the tablet excipients was found. The suitability of this method for the quantitative determination of telmisartan and metoprolol succinate was proved by validation. The proposed method was found to be simple and sensitive for the quality control application of telmisartan and metoprolol succinate in pharmaceutical dosage form. **Result:** The result of analysis has been validated statistically and by recovery studies. Recoveries were found in the range of 98.08-100.55% of telmisartan and 98.41-101.87% of metoprolol succinate.

Key words: Absorbance correction, metoprolol succunate, spectrophotometry, telmisartan

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INTRODUCTION

Telmisartan (TELM), 4′-[(1, 4′- dimethyl-2′-propyl [2, 6′-bi-1H benzimidazol]-1′-yl) methyl]-[1, 1′-biphenyl]-2-carboxylic acid, is an angiotensin II antagonist used as antihypertensive agent.[1-3] TELMI blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland.[4,5] Literature survey revealed that there are many developed methods on UV,[6-12] visible spectrophotometric,[13] HPTLC,[14,15] HPLC,[16] and UPLC[17] for estimation of TELM, single as well as in combination.

Metoprolol succinate (METO), 2-Propanol,1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]-(±) butanedioate succinate (2:1) (salt) is a cardioselective β-blocker used in the management of hypertension, angina pectoris, cardiac arrhythmias, myocardial infarction and heart failure.[18] Literature survey revealed that there are many developed methods on UV,[19-23] HPTLC,[24,25] HPLC,[26-31] for estimation of METO single as well as in combination.

However, there have been no reports concerning the simultaneous determination of (Figure 1) and (Figure 2) TELMI by absorbance correction method. These method was developed and validated as per International Conference on Harmonization (ICH) guidelines.[32]

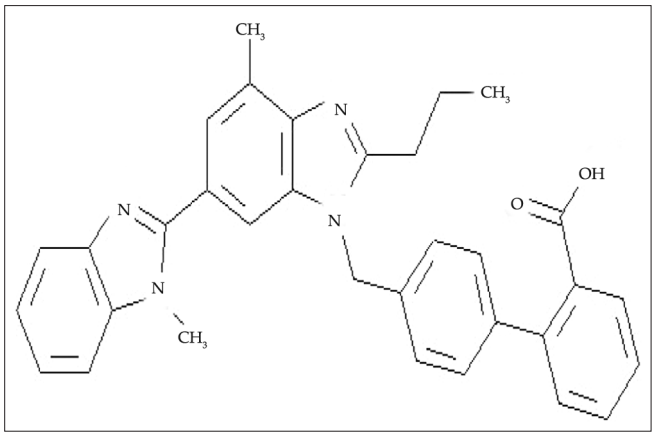

Figure 1: Chemical structure of Metoprolol succinate (METO)

MATERIALS AND METHODS

Apparatus

A shimadzu model 1800 (SHIMADZU CORPORATION, International Marketing Division, 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 2.31). Digital balance Acculab (ALC 210.4) and Sonicator Eneritech (Ultra Sonicator) was used in the study.

Material

Active pharmaceutical ingredient of TELM and METO were supplied by Zydus Cadila Healthcare Ltd., Ahmedabad, Gujarat, India.

Marketed formulation

TELSAR BETA (UNICHEM LABORATORIES, India) contains TELM IP 40 mg and METO USP 50 mg.

Other formulation Telmaxx 50 (GLENMARK pharmaceutical Ltd., Mumbai) was purchased from an open market for this study which contains TELM IP 40 mg and METO USP 50 mg [Table 3].

Reagent and chemical

Methanol was used as a solvent which was procured from Finar Chemicals Ltd., Ahmedabad, India. Double distilled water was used throughout the analysis.

Preparation of standard stock solution

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

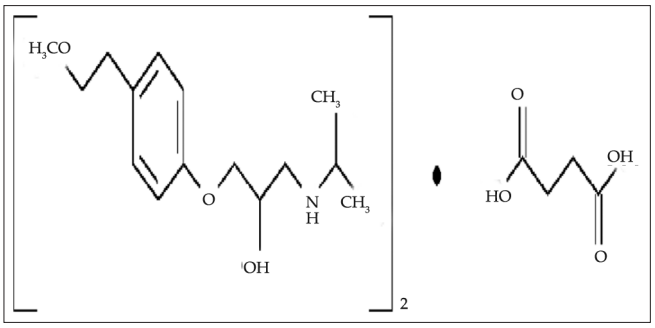

Figure 2: Chemical Structure of Telmisartan (TELM)

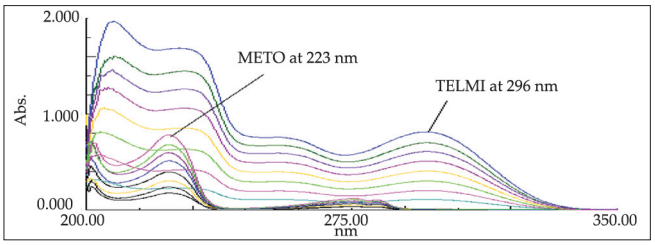

Figure 3: Simple overlay spectra of TELM (2-16µg/ml) and METO (3-24 µg/ml) in methanol

having concentration of TELM (100 µg/ml) and METO (100 µg/ml).

Absorbance correction method

The value of λ_{max} of was determined by scanning the drug solution in the range 200-400nm at 0.5 band width and 600 nm/min scan speed and was found to be at 296 nm and 223 nm, respectively. TELM also showed absorbance at 223 nm, while METO did not show any interference at 296 nm. [Figure 3] To construct Beer's plot for TELM and METO, stock solutions of both the drugs were prepared in methanol [100 µg/ml]. Also Beer's plot was constructed for TELM and METO in solution mixture at different concentration. Both the drugs followed linearity individually in TELM (2, 4, 6, 8, 10, 12, 14, 16 µg/ml) and METO (3, 6, 9, 12, 15, 18, 21, 24 µg/ml) and in mixture with the concentration range TELM:METO are (1:1.25, 2:2.5, 3:3.75, 4:5, 5:6.25, 6:7.5, 7:8.75 µg/ml).

The concentration of two drugs in the mixture can be calculated using following equations

$$A = abc$$
$$Cx = A1 / ab$$
$$Cx = A1 / ax1 * b \quad (1)$$

$$A2 = A\ Telm + A\ meto$$
$$A2 = (ay2 * cy * b) + (ax2 * cx * b)$$
$$A2 = (ay2 * cy) + (ax2 * cx)$$
$$Cy = [A2 - (ax2 * cx)] / ay2 \quad (2)$$

where A_1, A_2 are absorbance of mixture at 296 nm (λ_1) and 223 nm (λ_2), respectively, ax_1 and ax_2 are absorptivities of TELM at λ_1 and λ_2, respectively, ay_1 and ay_2 are absorptivities of METO at λ_1 and λ_2, respectively, c_x and c_y are concentrations of TELM and METO, respectively.

Validation of proposed method

Linearity (Calibration curve)

The calibration curves were plotted over a concentration range of 2-16 µg/ml for TELM and 3-24 µg/ml METO. Accurately measured standard stock solutions of each TELM (0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4 and 1.6 ml) and METO (0.3, 0.6, 0.9, 1.2, 1.5, 1.8, 2.1, 2.4) were transferred to a series of 10 ml volumetric flask separately and diluted up to the mark with methanol. The absorbances of solution were then measured at 296 nm and 223 nm. The calibration curves were constructed by plotting absorbances versus concentration and the regression equations were calculated.

Precision

System precision

Intraday

Mixed standard solutions containing 2, 4, 6 µg/ml TELM and 2.5, 5.0, 7.5 µg/ml of METO was analyzed three times on the same day. Measure the solution at 296 nm (A1) and 223 nm (A2). The results were reported in terms of relative standard deviation.

Interday

Mixed standard solution containing 2, 4, 6 µg/ml TELM and 2.5, 5.0, 7.5 µg/ml of METO was analyzed on 3 different days. Measure the solution at 296 nm (A1) and 223nm (A2). The results were reported in terms of relative standard deviation.

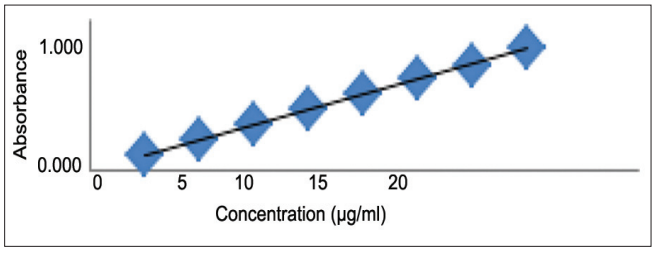

Figure 4: Calibration curve for TELM

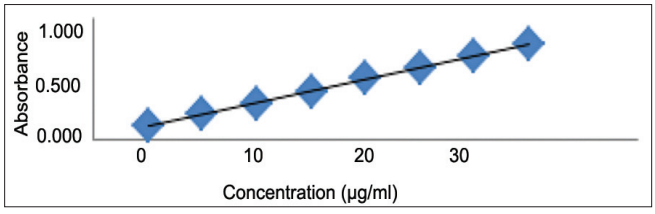

Figure 5: Calibration curve for METO

Method precision

Intraday

Test solutions containing 2, 4, 6 µg/ml TELM and 2.5, 5.0, 7.5 µg/ml of METO was analyzed three times on the same day. Measure the solution at 296 nm (A1) and 223 nm (A2). The results were reported in terms of relative standard deviation.

Interday

Test solution containing 2, 4, 6 µg/ml TELM and 2.5, 5.0, 7.5 µg/ml of METO was analyzed on 3 different days. Measure the solution at 296 nm (A1) and 223 nm (A2). The results were reported in terms of relative standard deviation.

Specificity

Specificity is a procedure to detect quantitatively the analyte in presence of component that may be expected to be present in the sample matrix. Commonly used excipients in tablet preparation were spiked in a preweight quantity of drug and then absorbance was measured and calculation done to determine quantity of drugs. [Figure 6]

Accuracy

The accuracy of the method was determined by calculating recoveries of TELM and METO by the standard addition method. Accuracy is performed at three levels 25, 50 and 75%. Known amount of standard solutions of TELM (0, 1, 2 and 3 µg/ml) and METO (0, 1.25, 2.5 and 3.75 µg/ml) were added to a pre-quantified test solution of TELM (4 µg/mL) and METO (5 µg/mL). Absorbance of solution was measured at selected wavelength for TELM and METO.

The amount of TELM and METO was calculated at each level by absorbance correction equation method and % recoveries were computed.

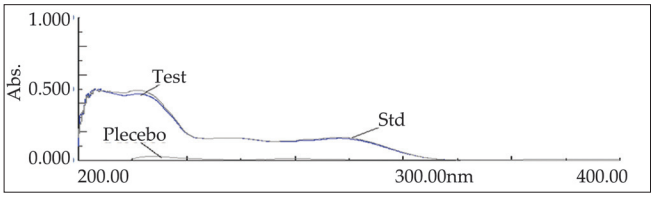

Figure 6: UV spectrum showing standard mixture of TELM and METO (4:5 µg/ml), test sample of TELM and METO (4:5 µg/ml), and placebo.

Limit of detection and limit of quantitation

Limit of detection is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value and limit of quantitation is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy.[32] For these prepare linearity at the lowest concentration mixture containing TELM (0.16 - 0.24 µg/ml) and METO (0.2 - 0.3 µg/ml) and measure The absorbance at 296 nm and 223 nm. Plot the calibration curve of absorbance vs concentration for individual wavelength and determine regression line equations for TELM and METO and find out the the limit of detection (LOD) and the limit of quantification (LOQ) were calculated using the standard deviation of repeatability and slope (S) of the calibration of new calibration curve for LOD and LOQ.

$$\text{LOD} = \frac{3.3 \times N}{S}$$

$$\text{LOQ} = \frac{10 \times N}{S}$$

where, N = the standard deviation of the response and S = slope of the calibration curve.

Analysis of TELM and METO in combined tablet

Twenty tablets were weighed and the average weight was calculated. The tablet powder equivalent to 10 mg of TELM and 12.5 mg of METO were 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 4 µg/ml of TELM and 5 µg/ml of METO. The absorbances of the sample solution i.e. A1 and A2 were recorded at 296 nm (λ-max of TELM) and 223 nm (λ-max of METO) respectively, Relative concentration of two drugs in the sample was calculated using above equation (1) and (2).

RESULTS AND DISCUSSION

In absorbance correction method, the primary requirement for developing a method for analysis is that the entire spectra should follow the Beer's law at all the wavelength,[16] which was fulfilled in case of both these drugs. The two wavelengths were used for the analysis of the drugs were 296 nm (λ-max of TELM) and 223 nm (λ-max of METO) at which the calibration curves were prepared for both the drugs. The overlain UV absorption spectra of TELM (296 nm) and METO (223 nm) in methanol is shown in [Figure 4 and 5]. The validation parameters were studied at all the wavelengths for the proposed method [Table 1]. Accuracy was determined by calculating the recovery and the mean was determined [Table 2]. The method was successfully used to determine the amounts of TELM and METO present in the tablet dosage forms. The results obtained were in good agreement with the corresponding labeled amount [Table 3]. Precision was calculated as repeatability and intra and interday variations (% RSD) for both the drugs.

CONCLUSIONS

The developed absorbance correction method is found to be simple, sensitive, accurate and precise and can

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

Parameters	TELM	METO
Wavelength range (nm)	296	223
Beer's law limit (µg/ml)	4-16	6-24
Regression equation (y = mx + c)	y = 0.050x + 0.003	y = 0.031x + 0.029
Slope	0.050	0.031
Intercept	0.003	0.029
Correlation Coefficient (r^2)	0.9999	0.9998
System precision (%R.S.D)[a]		
1. Intraday precision(*n* = 3)	0.79-1.45	0.17-0.53
2. Interday precision(*n* = 3)	0.66-1.46	0.20-0.72
Method precision (%R.S.D)		0.28-1.03
1. Intraday precision(*n* = 3)	0.48-1.45	0.23-0.92
2. Interday precision(*n* = 3)	0.96-1.49	
Accuracy (% recovery) (*n* = 3)	98.08-100.55%	98.41-101.87%
LOD[b] (µg/ml)	0.055	0.015
LOQ[c] (µg/ml)	0.166	0.045
Assay (±S.D.)[d] (*n* = 3)	99.0 ± 0.22	98.6 ± 1.12

[a]RSD = Relative standard deviation. [b]LOD = Limit of detection. [c]LOQ = Limit of quantitation [d]SD is Standard deviation and n is number of replicates.

Table 2: Recovery data of proposed method

Drug	Amount taken (µg/ml)	Amount added (µg/ml)	Amount added (%)	%Mean recovery (±S.D.) (*n* = 3)
TELM	4	1	25	99.74 ± 1.74
	4	2	50	98.08 ± 1.18
	4	3	75	100.55 ± 1.36
METO	5	1.25	25	101.87 ± 0.43
	5	2.5	50	100.13 ± 0.86
	5	3.75	75	98.41 ± 1.12

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

Table 3: Analysis of TELM and METO by proposed method

Tablet	Labelled claim (mg)		Amount found (mg)		% Label claim (±S. D.) (*n* = 3)	
	TELM	METO	TELM	METO	TELM	METO
I (TELSAR BETA)	40	50	39.60	49.30	99.00 ± 0.22	98.60 ± 1.12
II (Telmaxx 50)	40	50	39.51	49.27	98.77 ± 0.87	98.54 ± 1.23

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

be used for routine analysis of TELM and METO. The developed method was validated as par ICH guidelines. Statistical analysis proved that the method is repeatable and selective for the analysis of TELM and METO in combination as a single drug in bulk as well as in pharmaceutical formulations.

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