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Original Article

Spectrophotometric Simultaneous Equation and Area under the Curve Methods for Estimation of Metoprolol Succinate and Telmisartan in Pure Drugs and its Combined Marketed Formulation

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ABSTRACT

Background: Telmisartan-metoprolol succinate formulations treat hypertension. The primary goal was to develop and evaluate a UV-spectrophotometric method for estimating telmisartan and metoprolol succinate in a combination tablet dosage form in accordance with ICH standards. **Aim:** The study aimed to develop a simple, swift, precise, accurate and cost-effective UV spectrophotometric method for the simultaneous estimation of Telmisartan (TEL) and Metoprolol succinate (MET) in a combined tablet dosage form using Hydrochloric acid (HCl) and ethanol as solvents. **Materials and Methods:** Using HCl (0.1 N) and ethanol as solvents, the approach is predicated on simultaneous equations. MET has an absorbance maximum at 230 nm, while TEL is at 237 nm in its first-order spectrum. For Metoprolol succinate area range is between 229 and 213 nm, while for telmisartan it is between 304 and 277 nm, as determined by the area under the curve method. The reliability, precision, specificity, toughness and robustness of the suggested approach were all verified. Beer's rule was followed by metoprolol succinate and telmisartan between 5-25 µg/mL and 4-20 µg/mL, respectively, with a correlation coefficient value of 0.999. **Results:** Recovery experiments determined the accuracy of all methods and revealed recoveries between 98-100%. Interday and intraday precision were evaluated and the mean %RSD for all approaches was less than 2%. **Conclusion:** This study demonstrates that all parameters, including precision, recovery, accuracy and robustness, were met in accordance with ICH guidelines. The analysis's findings have been scientifically and statistically validated.

Keywords: Ethanol, Hydrochloric acid, Metoprolol succinate, Simultaneous equation, Telmisartan, Validation.

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INTRODUCTION

Chemically Metoprolol succinate [MET] is known as (RS)-1-(Isopropyl amino)-3-[4-(2-methoxyethyl) phenoxy] propane -2-ol succinate.[1] It is used as an oral β-adrenoceptor antagonist (β-blocker) for the treatment of cardiovascular diseases, especially hypertension. However, MET also inhibits β-2 adrenoreceptors at greater doses, which are mostly found in the bronchial and vascular musculature.[2] It can be used independently or in conjunction with other antihypertensive medications. Chemically Telmisartan [TEL] is known as 4'-{[4-methyl-6-(1-methyl-1H-benzimidazole-2-yl)-2-propyl-1H-benzimidazol-1-yl] methyl}-2-biphenyl-carboxylic acid used as angiotensin II receptor antagonist with antihypertensive properties.[3,4]

Combined formulations of these two drugs (Figure 1) are used for the treatment of hypertension.[5-11] Literature review shows that various methods are reported, such as spectrophotometric and HPLC, for the estimation of MET and TEL individually and simultaneously.[12,13] Hydrochloric acid (HCl) and ethanol as a diluent, spectroscopic approach have not been found in any literature surveys and neither AUC method has been reported. The present research aims to develop a simple, swift, precise, accurate and cost-effective UV spectrophotometric method for the simultaneous estimation of Telmisartan (TEL) and Metoprolol succinate (MET) in a combined tablet dosage form according to ICH guidelines.[14]

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MATERIALS AND METHODS

Instruments

-SHIMADJU UV-1800 double beam UV-visible spectrophotometer.

-Digital weighing balance (AUX220 Shimadzu, Japan).

-Ultrasonicator (model U311).

-pH meter (LABMAN LMPH10).

Chemicals and reagents

Telmisartan and Metoprolol Succinate were obtained as a gift sample from Macleods Pharmaceuticals Ltd., Baddi with a 99.99% w/w assay value and were used without further purification.

Marketed formulation

Telvas Beta®50 (Aristo Pharmaceuticals Pvt. Ltd., Baddi) contains TEL IP 40 mg and MET IP 50 mg was purchased from an open market. Hydrochloric acid (Sigma-Aldrich, USA) was prepared as a 0.1 N aqueous solution. Analytical-grade chemicals and reagents were used in all experiments. In all of our tests, we used water that had been twice distilled.

Preparation of Stock Solution

The standard stock solution of MET and TEL was prepared by dissolving 100 mg of each drug in 100 mL of HCl (0.1 N)+ethanol (1:1). Shake it properly to dissolve the drug and then adjust the volume with the same solvent to get 1000 µg/mL).

Preparation of Working Standard Solution

Working standard solutions of MET (100 µg/mL) and TEL (100 µg/mL) were prepared by transferring 5 mL aliquots to a 50 mL volumetric flask and then adjusting the volume with the same solvent.

Preparation of Calibration Curve of Standard MET and TEL

0.5, 1, 1.5, 2 and 2.5 mL Volumes were taken from the MET working standard solution (100 g/mL) and diluted to the correct concentrations in 10 mL volumetric flasks. The resulting MET concentrations are 5, 10, 15, 20 and 25 µg/mL. 0.4, 0.8, 1.2, 1.6 and 2 mL of the TEL working standard solution (100 g/mL) were transferred to 10 mL volumetric flasks and the rest of the volume was filled up with diluent. This produces concentrations of TEL at 4, 8, 12, 16 and 20 µg/mL. The samples were examined with a UV spectrophotometer and calibration graphs were created from the resulting data.[15]

Method 1-First derivative simultaneous equation method (Vierodt's method)

It was based on the absorption of drugs (X and Y) at the maximum wavelength.[8,16] Other quantification analyses of TEL and MET in the binary mixture were performed with the following equations and the results are illustrated in Figures 2-4.

$$C_x = \frac{A1\ ay2 - A2\ ay1}{ax1\ ay2 - ax2\ ay1} \quad \ldots\ldots\ldots\ldots\ (1)$$

$$C_y = \frac{A2\ ax1 - A1\ ax2}{ax1\ ay2 - ax2\ ay1} \quad \ldots\ldots\ldots\ldots\ (2)$$

Where; Cx and Cy are concentrations of TEL and MET respectively.

ax_1 and ax_2=Absorptivity of TEL at 230 and 237 nm; A_1 and A_2=Absorbances of the mixture at 230 and 237 nm.

ay_1 and ay_2=Absorptivity of MET at 230 nm and 237 nm.

Method 2-Area Under Curve (AUC) method

When there is no strong peak or when a wide spectrum is achieved, the AUC (Area Under Curve) approach can be used.[17-19]

Telmisartan (12 µg/mL) and metoprolol succinate (15 µg/mL) solutions were made using a diluent (0.1N HCl and ethanol) and the solutions were scanned in the ultraviolet spectrum from 200 to 400 nm. The wavelengths 304-277 nm and 229-213 nm were selected from the spectra to represent telmisartan and metoprolol succinate, respectively. The area under the curve technique was

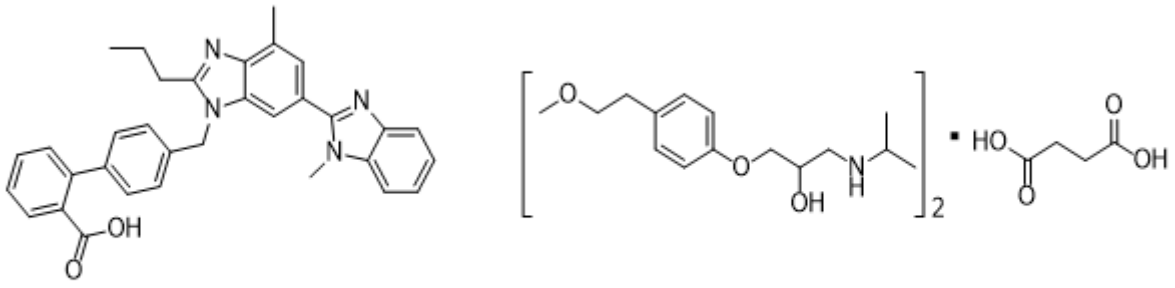

Figure 1: Chemical structure of Telmisartan (A) and Metoprolol Succinate (B).

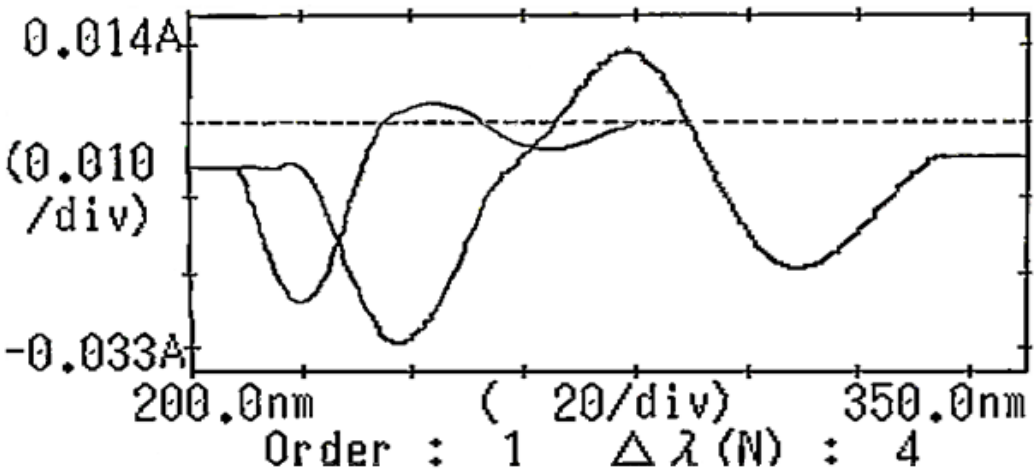

Figure 2: First-order overlay UV spectra of MET and TEL.

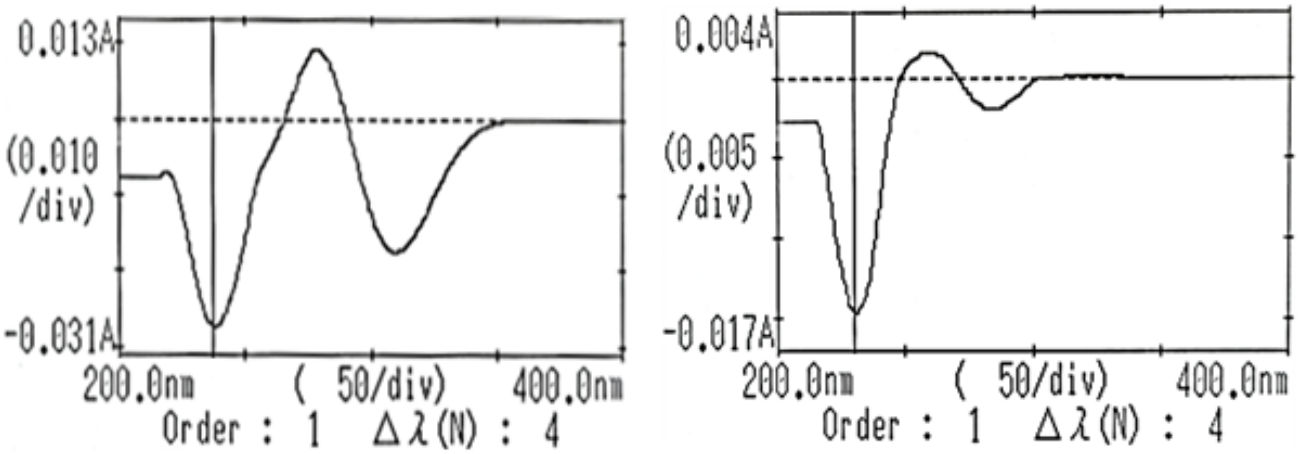

Figure 3: First derivative spectra of TEL and MET.

Table 1: Summary of validation parameters by proposed methods.

Parameters	Simultaneous equation (Method 1)		Area under the curve (Method 2)	
	MET	TEL	MET	TEL
Linearity range (µg/mL)	5-25	4-20	5-25	4-20
Regression equation	y=0.0076x+0.006	y=0.0935x+0.0576	y=0.4844x+0.2895	y=1.3518x+1.015
Regression coefficient (r^2)	0.9998	0.9997	0.9999	0.9999
Method Precision (%RSD)	0.66	0.05	0.43	0.12
LOD (µg/mL)	0.979	0.950	0.5612	0.6085
LOQ (µg/mL)	2.965	2.879	1.7008	1.8439
Robustness Analyst to Analyst (%RSD)	0.249-0.454	0.161-0.375	0.136-0.505	0.398-0.761
Robustness Lab to Lab (%RSD)	0.177-0.589	0.267-0.508	0.265-0.529	0.410-0.541

µ: micro, RSD: Relative Standard Deviation.

used to determine the concentrations of metoprolol succinate and telmisartan in these two spectral regions. Both medications' concentrations can be calculated using a single calculation by plugging in the integrated value of absorbance over the wavelength ranges of both drugs illustrated in Figures 5 and 6.

Validation Parameters

The suggested procedure has been validated in accordance with the standards set out by the International Conference on Harmonisation (ICH).[14,20-22] Descriptive statistics, including RSD and mean±standard deviation, were calculated.

Linearity and Range (Calibration Curve)

Calibration Curves were generated using the simultaneous equation approach and the area under the curve method for concentrations between 5-25 µg/mL of MET and 4-20 µg/mL of TEL, respectively, as discussed in Figures 4 and 5.[15]

Method precision (Repeatability)

The correctness of the instrument was evaluated by scanning the solution repeatedly (n=6) and measuring its absorbance (n=6) for TEL (4 µg/mL) and MET (5 µg/mL), without changing any of the first derivative spectrophotometry parameters as shown in Table 1.

Limit of Detection (LOD) and Limit of Quantitation (LOQ)

The results of the linearity tests were used to determine the LOD and LOQ illustrated in Table 1. Using the supplied formulae,[16,23] we calculated the ICH detection and quantitation limits by using the mentioned equation.

$$LOD=\frac{3.3\times\sigma}{S}$$

$$LOQ=\frac{10\times\sigma}{S}$$

Where,

σ=standard deviation of the response,

S= slope of the calibration curve (of the analyte).

Robustness

According to ICH, robustness is a gauge of a method's capacity to hold up against minor but deliberate changes in its input parameters. Parameters are tested 3 times (n=3) and results are discussed in Table 1. Instrument, laboratory and observer swaps were used to test the proposed method's stability.[14]

Intermediate precision (Reproducibility)

Inter-day and intra-day precision shows the reproducibility of the proposed methods. %RSD calculated from the assay of 3 replicates within a day is known as intra-day precision whereas %RSD calculated from the assay of 3 replicates on 3 consecutive days shows its inter-day precision as discussed in Table 2.

Table 2: Intra-day and Inter-day Precision study of the proposed methods.

Precision	Intra-day Precision					
	Telmisartan			Metoprolol		
	Conc. (µg/mL)	% Amount found*	%RSD	Conc. (µg/mL)	% Amount found*	%RSD
Method 1	4	99.84	0.52	5	98.60	0.40
	8	99.08	0.19	10	99.27	0.32
	12	99.49	0.51	15	99.63	0.15
Method 2	4	98.97	0.39	5	99.14	0.60
	8	98.87	0.40	10	99.26	0.34
	12	99.19	0.71	15	99.07	0.48
Inter-day Precision						
Method 1	4	99.00	0.66	5	98.87	0.42
	8	99.12	0.37	10	99.27	0.76
	12	99.47	0.38	15	99.58	0.23
Method 2	4	99.08	0.48	5	99.24	0.62
	8	98.84	0.39	10	99.01	0.74
	12	99.27	0.45	15	99.08	0.50

* Mean of 3 observations, RSD: Relative Standard deviation.

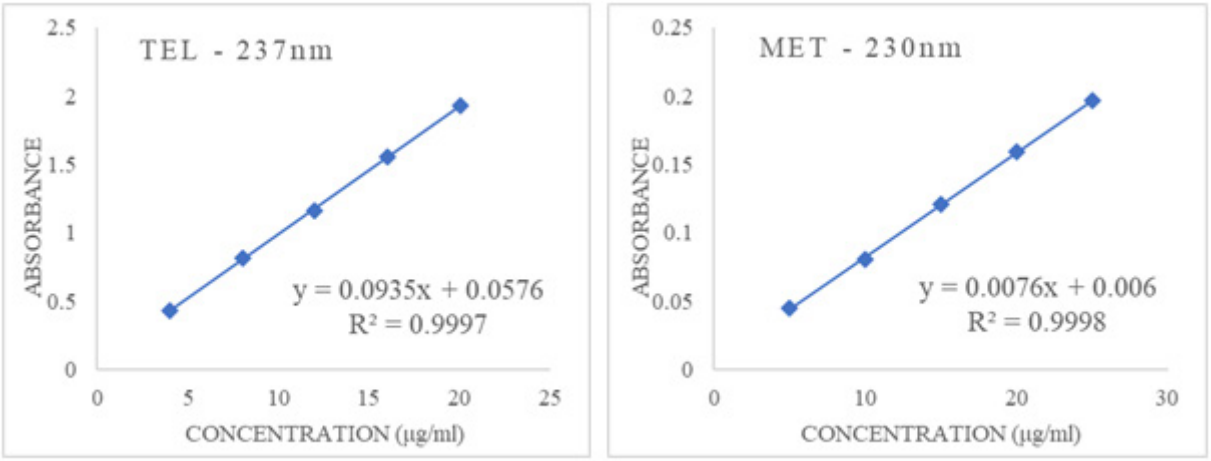

Figure 4: Calibration graph of TEL and MET by First derivative simultaneous method.

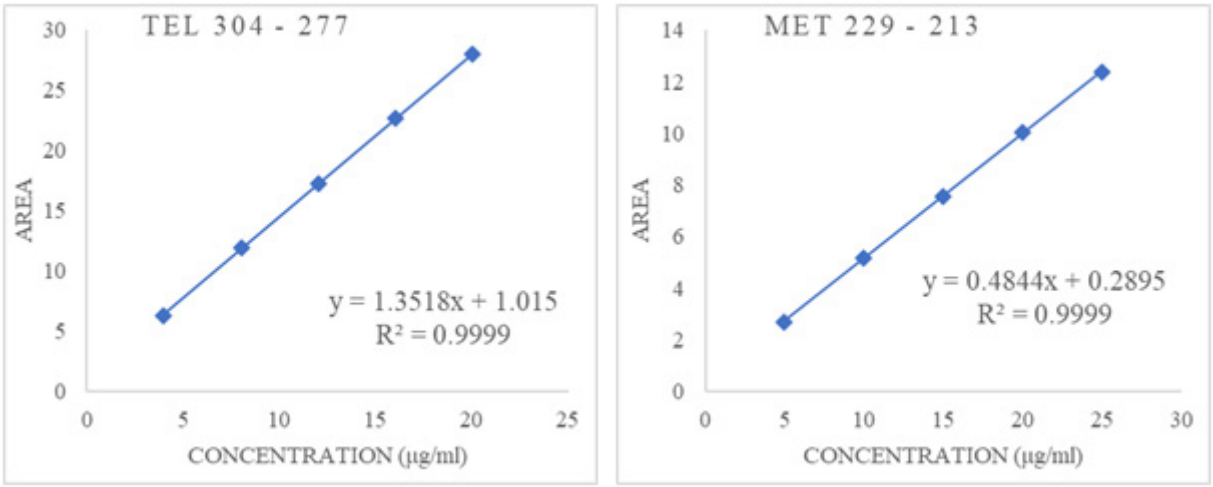

Figure 5: Calibration graphs of TEL and MET by Area Under Curve method.

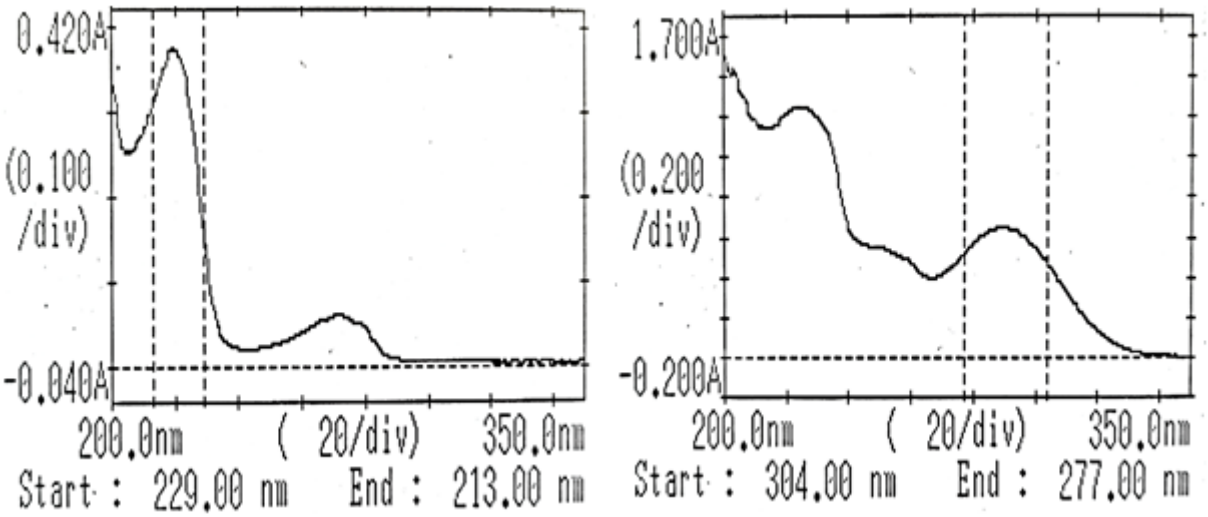

Figure 6: UV Area under curve spectrum of TEL and MET.

Accuracy (Recovery study)

The accuracy of the process was used by calculating TEL and MET recovery using the conventional addition method. The amount of TEL and MET was calculated at each level by simultaneous equation methods as well as the area under curve method and %recovery was calculated as discussed in Table 3.

Analysis of TEL and MET in combined Marketed Formulation

Twenty Telvas βeta®50 tablets with 50 mg of Metoprolol succinate and 40 mg of Telmisartan were accurately weighed to establish the average weight as discussed in Table 4. The tablet powder equivalent to 10 mg of telmisartan and 12.5 mg of metoprolol succinate was weighed and transferred into a 100 mL volumetric flask. A minimum amount of diluent was added to dissolve the material and make up the volume (100 µg/mL for TEL and 125 µg/mL for MET). After 15 min of sonication, the mixture was centrifuged at 100 rpm and filtered with Whatman filter paper. From the clear solution, 1 mL was transferred to a 25 mL volumetric flask and filled with 0.1N HCl and ethanol to get 4 µg/mL of telmisartan and 5 µg of metoprolol succinate.[24,25]

RESULTS

Calibration curves were generated and regression equations were determined using the simultaneous equation and area under curve approach, as shown in Figures 2-6. %RSD, LOD and LOQ were calculated and the robustness of the proposed methods was established on the basis of a low %RSD value as discussed in Table 1. The findings of intra-day, inter-day precision and Accuracy data are summarised in Tables 2 and 3. Proposed assay methods were used for the evaluation of the marketed formulation for its labelled claim, as discussed in Table 4.

DISCUSSION

Most active compounds absorb in the UV, however spectrophotometric methods are the easiest, fastest and most applicable to all labs. The 1st derivative simultaneous equation and area under the curve are used to analyse MET and TEL in combination tablets.

For the First derivative simultaneous equation and AUC methods

With a UV spectrophotometer, the standard solution absorbance was measured to determine linearity. MET and TEL were dissolved in 0.1N HCl and ethanol as sample solutions. Calibration curves were created by plotting concentration vs. absorbance for both drugs at 237 nm (λ_{max} of TEL) and 230 nm (λ_{max} of MET) and for the AUC method, 229-213 nm for MET and 304-277 nm for TEL (see Figures 4 and 5). Beer's law conformance is shown by linear calibration curves and correlation coefficients of 0.9997 for TEL and 0.9998 for MET discussed in Table 1. The suggested procedures were validated following ICH guidelines.[14] Results showed that LOD and LOQ for the simultaneous method were 0.979 µg/mL and 2.96 µg/mL for MET and for TEL were 0.95 µg/mL and 2.87 µg/mL respectively. As shown in Table 1, LOD and LOQ for the AUC method were 0.56 g/mL and 1.70 µg/mL for MET respectively and for TEL were 0.608 µg/mL and 1.84 µg/mL. The accuracy and precision of the data presented in Tables 2 and 3 were maintained across the whole concentration range. The %RSD value for drugs is less than 2, indicating that this method is precise. The validity of the proposed procedure is evaluated further by employing the standard addition technique, which

Table 3: Accuracy data of determination of Telmisartan and Metoprolol using first Derivative Spectroscopy and area under curve method.

Method	Drug	Percentage (%)	Drug taken (Formulation) (µg/mL)	Drug added (Pure Drug) (µg/mL)	Total amount found* (µg/mL)	%Mean recovery ±S.D. (*n*=3)
1	TEL	50	4	2	5.92	98.72±0.75
		100	4	4	7.96	99.54±1.18
		150	4	6	9.96	99.63±1.02
	MET	50	5	2.5	7.49	99.82±0.85
		100	5	5	9.92	99.46±1.16
		150	5	7.5	12.47	99.74±0.85
2	TEL	50	4	2	5.90	98.34±0.60
		100	4	4	7.95	99.46±1.20
		150	4	6	9.94	99.48±1.15
	MET	50	5	2.5	7.48	99.74±0.80
		100	5	5	9.99	99.94±0.58
		150	5	7.5	12.37	98.96±0.21

*Mean of 3 observations.

Table 4: Analysis of marketed formulation.

Formulation Brand Name: Telvas βeta®50			
Labelled claim: TEL: MET (40 mg:50 mg)			
Method	**Drug**	**Amount found (mg)**	**%Label claim (±S.D.) (*n*=6)**
1	Telmisartan*	39.73	99.33±0.05
	Metoprolol *	49.96	99.93±0.66
2	Telmisartan*	39.96	99.91±0.13
	Metoprolol*	49.85	99.69±0.44

*Mean value of 6 determinations.

reveals no interference from excipients. The obtained results are displayed in Table 3. For quantification, the % purity of tablets was found to be 99.93±0.66 and 99.33±0.05 for metoprolol succinate and telmisartan respectively, for the simultaneous equation method. In the case of AUC method, the percentage purity of the tablets was found to be 99.69±0.44 and 99.91±0.13 for metoprolol succinate and telmisartan respectively. The results found agreed well with their labelled counterparts as illustrated in Table 4.

CONCLUSION

In contrast to the most commonly recommended HPLC procedures, the proposed spectrophotometric methods, simultaneous estimation and area under the curve for metoprolol and telmisartan were simple, robust, accurate and precise in accordance with ICH guidelines and can be used for bulk drug and pharmaceutical dosage formulation assay. This formulation quantification approach is validated. The sample recoveries in all formulations matched their label claims, facilitating routine evaluation of pure drug or pharmaceutical formulations. The suggested approaches were therefore determined to be both cost-effective and suitable for routine quality control of combination dose formulations of metoprolol and telmisartan in the future.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

MET: Metoprolol Succinate; **TEL:** Telmisartan, **β:** Beta; **HCl:** Hydrochloric acid; **AUC:** Area under the curve; **IP:** Indian Pharmacopoeia; **µ:** Micro**; λ:** Lambda; **RSD:** Relative standard deviation; **LOD:** Limit of Detection; **LOQ:** Limit of Quantitation; **UV:** Ultraviolet; **HPLC:** High-pressure liquid chromatography; **ICH:** International Conference on Harmonization.

SUMMARY

The Simultaneous equation and the area under the curve method were developed for this study because spectroscopic techniques are effective and convenient for assessment. This new approach is precise, reliable and reasonably priced. Based on the results, it is clear that the suggested and validated method can be used for regular analysis of Telmisartan and Metoprolol Succinate in research laboratories and in the pharmaceutical industry, both in bulk and in their respective dose forms.

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