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Short Communication

SIMULTANEOUS QUANTIFICATION OF TELMISARTAN AND METOPROLOL SUCCINATE IN TABLETS BY LIQUID CHROMATOGRAPHY

K. Pravalika[1], Madhusudhanareddy Induri[2], M. Sudhakar[3]

[1]Department of Pharmaceutical Analysis, [2]Department of Pharmaceutical Chemistry, [3]Department of Pharmaceutics, Malla Reddy College of Pharmacy, Maisammaguda, Dhulapally, Secunderabad, Andhra Pradesh, India-500014

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ABSTRACT

An accurate and precise liquid chromatographic method was developed for the simultaneous estimation of telmisartan and metoprolol succinate in tablets. The chromatographic analysis was performed on Nucleosil C18 Column (250*4.6mm 5µ particle size) with mobile phase consisting of acetonitrile and potassium di-hydrogen orthophosphate buffer (pH- 2.8) in the ratio 60:40v/v, at a flow rate of 0.8ml/min and eluents monitored at 220nm. The retention time for telmisartan was found to be 3.392 and for metoprolol succinate it was found to be 5.221 minutes. The proposed method is simple, accurate and precise and could be successfully employed in routine quality control for the simultaneous estimation of telmisartan and metoprolol succinate in tablets.

Keywords: Telmisartan, metoprolol succinate, RP-HPLC

INTRODUCTION

Telmisartan, chemically 4¹-[(1,4¹-dimethyl-2¹-propyl[2,6¹-bi-1H benzimadazole]-1¹-yl) methyl]-[1,1¹-bipenyl]-2-carboxylic acid. Telmisartan is an angiotensin II receptor antagonist. It is used in the management of hypertension. Telmisartan 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 [1-6].

Metoprolol succinate, chemically 2-propanol, 1-[4-(2-methoxyethyl) phenoxy]-3-[(1-methyethyl) amino]-(±) butanedioate succinate. Metoprolol succinate is a cardioselective β-blocker. It is used in management of hypertension, angina pectoris, cardiac arrhythmia, myocardial infarction and heart failure [7-9]. A survey of pertinent literature revealed that few spectrophotometric [10-12] methods. Absorbance correction method has been reported for estimation of telmisartan and metoprolol succinate in combined tablet dosage forms [13].Normal and reverse phase HPTLC method has been reported for simultaneous estimation of telmisartan and metoprolol succinate in pharmaceutical formulation [14]. Three HPLC methods [15-17] have been reported for the simultaneous estimation of telmisartan and metoprolol in dosage form.

But the reported methods lack in chromatographic resolution, sensitivity and peak symmetry. Present study involves development and validation of HPLC method for the simultaneous estimation of telmisartan and metoprolol succinate in combined tablet dosage form, which is sensitive with better resolution and peak symmetry.

MATERIALS AND METHODS

Materials: Pure telmisartan (TELM) and metoprolol (METO) used as working standards, were gifts from Dr.Reddy's Labs., Hyderabad, India. Methanol and water (HPLC-grade) were purchased from Rankem, India. All other chemicals and reagents employed were of analytical grade, and purchased from Merck, India. Oral tablets containing 47.5mg of metoprolol succinate and 40mg of telmisartan (Teliprolol) were obtained from local pharmacies and used within their shelf life period.

***Corresponding Author Address:** K. Pravalika, Department of Pharmaceutical Analysis, Malla Reddy College of Pharmacy, Maisammaguda, Dhulapally, Secunderabad, Andhra Pradesh, India-500014, E-mail: pravalika.july10@gmail.com*

Instrumentation: The chromatographic system comprised of Waters 2695 binary gradient pump, with in-built auto sampler, column oven and Waters 2487 dual wavelength absorbance detector (DAD). Data integration was carried out using Empower-2 software. Samples were injected into Nucleosil C_{18} Column (250*4.6mm 5µ particle size). A Bandline sonerex sonicator was used for enhancing the dissolution of the compounds. A Digisum DI 707 digital pH meter was used for pH adjustment.

Chromatographic conditions: The high performance liquid chromatographic (HPLC) system was operated isocratically with the column temperature maintained at ambient, using a mobile phase composition of acetonitrile and potassium di-hydrogen orthophosphate buffer (pH adjusted to 2.8 with orthophosphoric acid) in the ratio of 60:40%v/v at a flow rate of 0.8mL/min within a run time of 10min. Prior to use, the mobile phase was degassed by an ultrasonic bath and filtered by a millipore vaccum filter system equipped with 0.45µm high vaccum filter. Both drugs were detected at 220nm.

Preparation of standard solutions: The standard solutions were prepared by transferring 100mg of telmisartan and 100mg of metoprolol succinate working standards into 100mL volumetric flask. To each, 30mL methanol was added, and the mixture was sonicated to dissolve and make up the volume with methanol. Aliquots of the standard solutions were transferred using A-grade bulb pipettes into 100mL volumetric flasks and the solutions made up to the volume with mobile phase to give a final concentration of 8.42-42.11 µg/mL of telmisartan and 10-50 µg/mL metoprolol succinate, respectively.

Quantification of telmisartan and metoprolol succinate from tablets: Twenty tablets were accurately weighed and crushed to a fine powder in a mortar. An amount of the powder equivalent to one tablet was transferred into a 100ml volumetric flask and 30ml of methanol was added to it. The mixture was sonicated to dissolve and then made up to volume with methanol. Following 25min of mechanical shaking, it was kept in an ultrasonic bath for 5min, and the solution filtered through 0.45 µm filter paper. Suitable aliquots of the filtered solution were transferred to a volumetric flask and made up to volume with mobile phase to yield concentrations of telmisartan (25.2µg) and metoprolol succcinate (30µg). A 20mL volume of the sample solution was injected into the chromatographic system, six times, under optimized chromatographic conditions. The peak areas were measured at 220nm.

Method validation: The method was validated in accordance with ICH guidelines. The parameters assessed were linearity, accuracy, limit of detection (LOD), limit of quantification (LOQ), precision, reproducibility, robustness and system suitability [18].

RESULTS AND DISCUSSIONS

The RP-HPLC method, as described was validated and successfully employed for the simultaneous quantification of telmisartan and metoprolol succinate in tablets. There is need to consider the successive steps for the development of RP-HPLC method. In particular, the problems relating to the standardization of sample preparations and selection of mobile phase needs to be emphasized. The optimized chromatographic conditions were selected based on sensitivity, retention time, peak shape and baseline drifts. The method was selective for the determination of telmisartan and metoprolol succinate since no interfering peaks appeared near the retention time of the compound of interest. A typical chromatogram recorded at 220nm is shown in Figure 1. The retention times of telmisartan and metoprolol succinate at a flow rate of 0.8mL/min were 3.392 and 5.221 min respectively. The analyte peaks were well resolved and were from tailing (< 2 for both the analytes). To ensure the validity of a system and analytical method, system suitability test was performed. The percent relative standard deviation (%RSD) of the retention times (t_R) and the peak areas of telmisartan and metoprolol from the six consecutive injections of the standard solutions were injected. The tailing factor for telmisartan and metoprolol succinate peaks were 1.67 and 1.32, respectively, thus reflecting good peak symmetry. The resolution (Rs) between telmisartan and metoprolol succinate was 3.48, indicating good separation of both analytes from each other. The theoretical plate no. for telmisartan and metoprolol were 2761 and 2110, respectively, thus indicating good column efficiency (Table 1). The results for linearity were shown in Table 1. The calibration curve obtained by plotting peak area against concentration showed linearity in the concentration range of 10-50µg/ml for metoprolol and 8.42-42.11µ/ml for telmisartan. The regression coefficients of telmisartan (r^2 =0.9998) and metoprolol succinate (r^2 =0.9995) indicate a good linear relationship between peak area versus concentration over a wide range. LOD for metoprolol succinate and telmisartan was 0.57 and 0.60µg/mL , respectively, while LOQ was 1.75 and 1.83µg/mL , respectively (Table 1).

Results for intra and inter assay precision, expressed as %RSD, results were given in Table 3. The low values of %RSD indicate that the method is precise. Reproducibility was checked by analyzing the samples by another analyst using same instrument and same laboratory. There was no significant difference between %RSD values, which indicates that the proposed method was reproducible. There was no significant change in the peak areas and retention times of telmisartan and metoprolol succinate when the organic strength and the pH of buffer were changed. The low values of %RSD indicate that the method was robust (Table 4). The method was robust as minor changes in the chromatographic parameters did not bring about any significant changes in peak area and retention time. The proposed method was applied to the simultaneous determination of telmisartan and metoprolol succinate in tablets. The results of the assay yielded for telmisartan and for metoprolol succinate, of label claim of the tablets. The assay results show that the method was selective for the simultaneous determination of telmisartan and metoprolol succinate without the interference from the exceipients used in the tablet dosage form and the results were shown in the Table 5.

CONCLUSION

The developed method for the simultaneous determination of telmisartan and metoprolol succinate has the advantages of sensitivity, accuracy, precision. The non-interference of tablet exceipients makes the method suitable for the determination of these drugs in tablets, and hence can be used for routine quality control of telmisartan and metoprolol succinate in this dosage form.

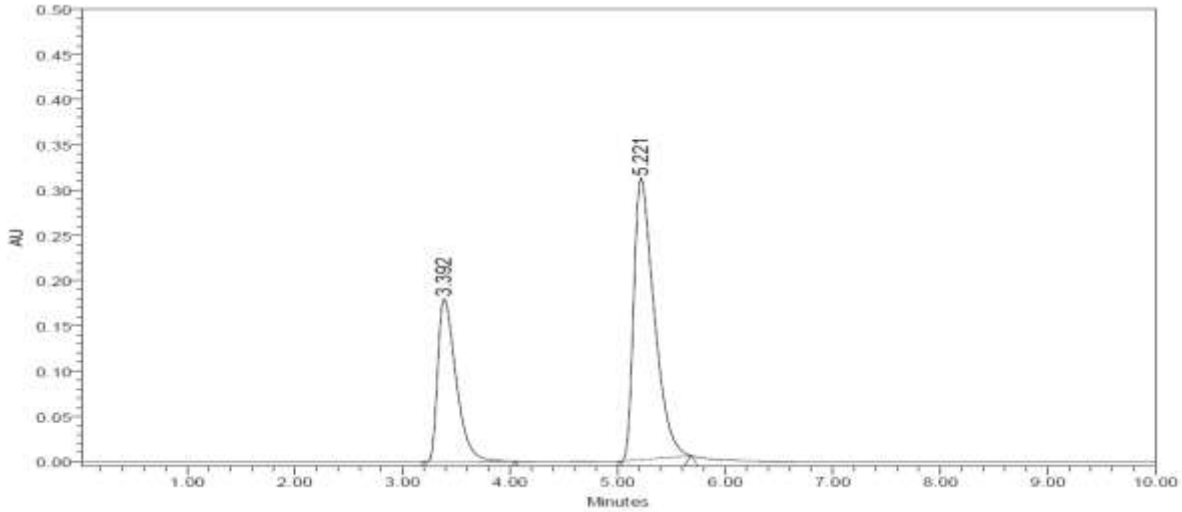

Figure 1: A typical chromatogram of telmisartan (t_R: 3.392) and metoprolol succinate (t_R: 5.221)

Table 1: System suitability parameters and linearity data for proposed method

Validation parameters	Results	
	Metoprolol succinate	Telmisartan
Linearity	10-50µg/mL	8.42-42.11µg/mL
Regression line	y=11557x+11488	y=52408+55061
Regression coefficient (r^2)	0.9995	0.9998
Limit of detection (µg/mL)	0.57	0.60
Limit of quantitation (µg/mL)	1.75	1.83
System suitability parameter*		
Peak area (%RSD)	1.42	1.21
Retention time (%RSD)	0.95	1.32
Tailing factor	1.67	1.32
Number of theoretical plates	2761	2110
Resolution	3.48	

*Replicates of six determinations

Table 2: Results of recovery studies by standard addition method

Analyte	Amount of Standard drug spiked		Amount of sample taken (mg)	% Recovery (Mean± SD)	RSD (%)	SEM
	% Spiked	mg				
MET	50	5	10	99.34±0.84	0.85	0.4859
	100	10	10	100.79±0.41	0.41	0.2364
	150	15	10	99.36±1.17	1.17	0.6727
TEL	50	4.21	8.42	99.72±1.43	1.43	0.8279
	100	8.42	8.42	99.49±1.12	1.12	0.6447
	150	12.63	8.42	101.43±0.78	0.78	0.4479

Table 3: Precision data of the proposed method

Analyte	Analyte conc. (µg/mL)	Intra-assay Precision*	Inter-assay Precision*	Reproducibility*	
				Analyst one	Analyst two
TELM	12.63	0.84	1.65	0.89	1.54
	16.84	1.43	1.04	0.37	1.34
	21.05	1.73	0.89	0.96	0.89
METO	15	0.36	1.34	1.07	1.63
	20	1.02	1.09	1.67	1.42
	25	0.92	1.67	0.58	1.38

*%RSD Values

Table 4: Results for robustness of the proposed method

Parameter	Original	Used	Analyte	Peak area		Retention time	
				Mean± SD	*RSD*	*Mean± SD*	*RSD*
Organic phase	60	58	Met	2071885±*122*	0.59	5.174±*0.0281*	0.54
		60		2106592±*107*	0.51	5.161±*0.0519*	1.01
		62		2044674±*252*	1.23	5.099±*0.0881*	1.73
		58	Tel	4237028±*459*	1.08	3.211±*0.0573*	1.78
		60		4103589±*833*	0.20	3.296±*0.0264*	0.80
		62		3876797±*563*	1.45	3.429±*0.0503*	1.47
Flow rate	0.8	0.7	Met	2363319±*319*	1.35	5.458±*0.0654*	1.20
		0.8		2116988±*871*	0.41	5.263±*0.0418*	0.79
		0.9		2067509±*285*	1.38	4.955±*0.0434*	0.88
		0.7	Tel	4114400±*781*	1.90	3.504±*0.0191*	0.54
		0.8		4110062±*194*	0.47	3.294±*0.0085*	0.26
		0.9		4388183±*681*	1.55	3.163±*0.0306*	0.97

Table 5: Assay results for Telmisartan and Metoprolol succinate in tablets

Product	Analyte	Labelclaim per tablet(mg)	% analyte estimated (Mean±SD)	RSD (%)	SEM
Teliprolol	Telmisartan	40	99.51±1.0715	1.08	0.4374
	Metoprolol Succinate	47.5	100.23±0.7994	0.80	0.3263

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