Original Article

Validated spectrophotometric methods for the simultaneous determination of telmisartan and atorvastatin in bulk and tablets

Abstract

Aim: Three simple, accurate, and reproducible spectrophotometric methods have been developed and validated for simultaneous estimation of telmisartan (TELM) atorvastatin (ATV) in combined tablet dosage form. **Materials and Methods:** The first method is based on first-order derivative spectroscopy. The sampling wavelengths were 223 nm (zero crossing of TELM) where ATV showed considerable absorbance and 272 nm (zero crossing of ATV) where TELM showed considerable absorbance. The second method Q-analysis (absorbance ratio), involves formation of Q-absorbance equation using respective absorptivity values at 280.9 nm (isobestic point) and 296.0 nm (λmax of TELM). The third method involves determination using multicomponent mode method; sampling wavelengths selected were 296.0 and 246.9 nm. **Results**: TELM and ATV followed linearity in the concentration range of 5–40 and 4–32 μg/ml for method I, 5–30 μg/ml and 2–24 μg/ml for method II and III, respectively. Mean recoveries for all three methods were found satisfactory. All methods were validated according to International Conference on Harmonization Q2B guidelines. **Conclusion:** The developed methods are simple, precise, rugged, and economical. The utility of methods has been demonstrated by analysis of commercially available tablet dosage form.

Key words: Absorbance ratio, atorvastatin, derivative spectroscopy, multicomponent analysis, telmisartan

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INTRODUCTION

Telmisartan (TELM) chemically 4′-[(1, 4′-Dimethyl–2′-propyl-[2, 6′-bi-1H-benzimidazol]-1′-yl) methyl]-[1, 1′-biphenyl]-2-carboxylic acid, is a nonpeptide angiotensin-II receptor antagonist, which selectively and insurmountably inhibits angiotensin-II AT1 receptor subtype without affecting other systems involved in cardiovascular regulation [Figure 1]. Atorvastatin (ATV) calcium chemically [R-(R*, R*)]-2-(4-fluorophenyl)-β, δ, dihydroxy-5-(1-methyl ethyl)-3-phenyl-4 [(phenyl-amino)-carboxyl]-1 H-pyrrole-1-heptanoic acid calcium salt is a second generation synthetic 3-hydroxy-3-methyl glutaryl-coenzyme A (HMG-CoA) reductase inhibitor, which decreases *de novo* cholesterol synthesis [Figure 2]. ATR decreases the amount of low-density lipoprotein (LDL)-cholesterol in blood, reduces blood levels of triglycerides and slightly increases levels of high-density lipoprotein (HDL)-cholesterol.[1-3] Literature survey reveals several methods for determination of TELM and ATV individually in biological fluids and formulation like HPLC, TLC-densitometric, and derivative spectrophotometry.[4-14] HPLC and HPTLC methods were reported for determination of TELM and ATV in combination.[15,16]

However, due to lack of such equipments in many resources-limited countries and high costs of HPLC grade solvents and columns, alternative methods are needed to facilitate and increase the speed of analysis, with relatively few costs. Spectrophotometry continues to be very popular, because of its simplicity, versatility and low cost. In this paper, a successful attempt has been

made to estimate two drugs simultaneously by UV spectrophotometric analysis. This paper describes three simple, rapid, accurate, reproducible, and economical methods for simultaneous determination of TELM and ATV in tablet formulation using first order derivative, Q-analysis, and multicomponent mode method.

MATERIALS AND MEHODS

Chemicals and reagents

Pharmaceutical grade TELM and ATV were supplied by Atoz laboratories, Chennai, India. Tablets labeled to contain 40 mg TELM and 10 mg ATV were manufactured and supplied by Dr. Reddy's Laboratories Ltd., Hyderabad, India. Methanol (analytical grade) was obtained from Merck Chemicals, Mumbai, India.

Equipment

A double beam UV/Visible spectrophotometer (Schimadzu, Japan) model UV-1700 with quartz cell 1 cm path length, connected to HP computer version 2.21 was used. Shimadzu balance (AUW-120D) was used for all weighing.

Standard stock solution

Standard stock solution (1.0 mg/ml) each of TELM and ATV was separately prepared by dissolving in methanol. These stock solutions were further diluted to get working standard stock solutions (each 100 μg/ml).

Sample preparation

Twenty tablets were accurately weighed and tablet powder equivalent to 100 mg of TELM was transferred into a 100 ml volumetric flask; 50 ml methanol was added, dissolved and completed to 100 ml with same solvent. The resulting solution is filtered through Whatmann filter paper, discarding first few millilitres. From the above solution suitable aliquots were completed to volume with methanol to get concentration in the ratio of 4:1, taking into consideration its amount present in combined tablet formulation.

Method I

First order derivative spectroscopy

The first derivative (D1) spectra of TELM and ATV was found to show zero crossing point and assisted in their simultaneous estimation [Figure 3]. First

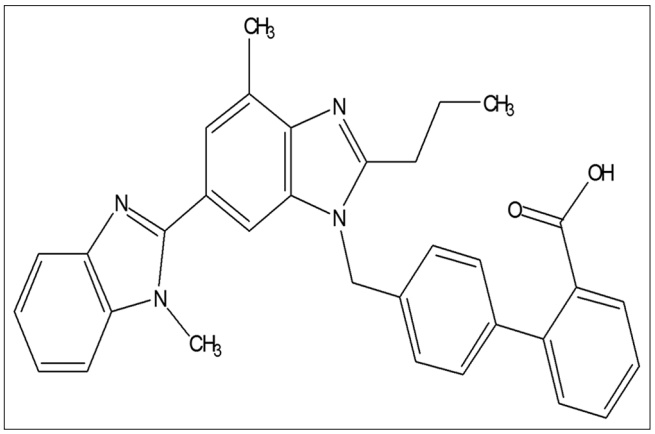

Figure 1: Chemical structure of telmisartan

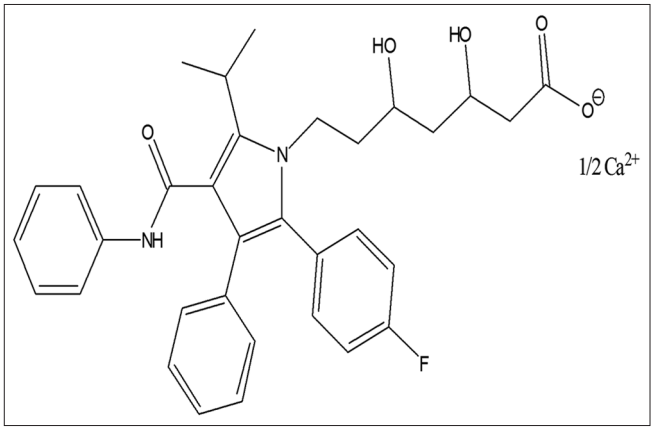

Figure 2: Chemical structure of atorvastatin calcium

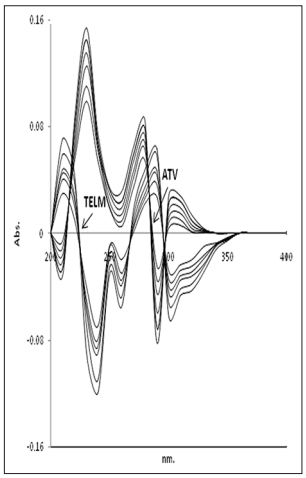

Figure 3: First order derivative spectra of TELM and ATV for different linear concentrations

derivative values of TELM and ATV were measured at 272 and 223 nm. Calibration curves were constructed by analysis of working standard solutions of TELM and ATV with six different concentrations in the range between 5–40 and 4–32 μg/ml for TELM and ATV, respectively. Each concentration was analyzed

thrice. In assay of tablet formulation, the sample solution of final concentration 20 μg/ml of TELM and 5 μg/ml of ATV was analyzed by first-order derivative spectroscopic method. The absorbance was measured at 272 and 223 nm. The procedure was repeated five times for sample analysis. The concentration of TELM and ATV were calculated from calibration graph.

Method II

Q-analysis method (Absorbance ratio)

Zero order absorption spectra of TELM shows λ_{max} at 296.0 nm [Figure 4]. Similarly, ATV shows λ_{max} at 246.9 nm [Figure 5]. For Q-analysis, the absorption spectra of prepared solutions were recorded in the range of 200–400 nm and absorbance values at 296.0 nm (λ_{max} of TELM) and 280.9 nm (isobestic point) were measured [Figure 6]. The absorptivity values for both drugs at selected wavelengths were calculated and the average values were taken. The method employs Q values and the concentrations of both drugs were determined using following equation.

$$Cx = (Qm - Qx/Qx - Qy) \times A1/ax1 \quad (1)$$

$$Cy = (Qm - Qy/Qy - Qx) \times A1/ay1 \quad (2)$$

where Cx and Cy are concentrations of TELM and ATV in μg/ml, respectively, Qm is absorbance of sample at 296.0 nm/absorbance of sample at 280.9 nm; Qx is absorptivity of TELM at 296.0 nm/absorptivity of TELM at 280.9 nm; Qy is absorptivity of ATV at 296.0 nm/absorptivity of ATV at 280.9 nm; ax1 is absorptivity of TELM at 280.9 nm; ay1 is absorptivity of ATV at 280.9 nm; and A1 is absorbance of the sample at 280.9 nm. The absorbance of laboratory prepared mixtures at 296.0 and 280.9 nm were recorded; absorptivity were calculated and substituted in the equations mentioned above, in order to obtain the concentration of both drugs.

Method III

Multicomponent mode method

For this method 296.0 nm (λ_{max} of TELM) and 246.9 nm (λ_{max} of ATV) were selected as two sampling wavelengths for TELM and ATV and multicomponent mode of spectrophotometer was used. Similarly, sample solutions were scanned in the multicomponent mode of instrument at selected sampling wavelengths [Figure 7]. The overlain spectra of five standard binary mixtures were employed to determine the concentration of drugs in sample solutions by analysis of spectral data of sample solutions with reference to mixture standards.

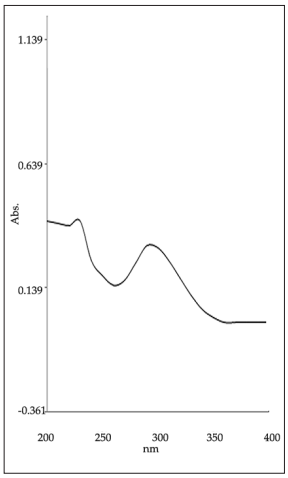

Figure 4: Zero order absorption spectra of TELM

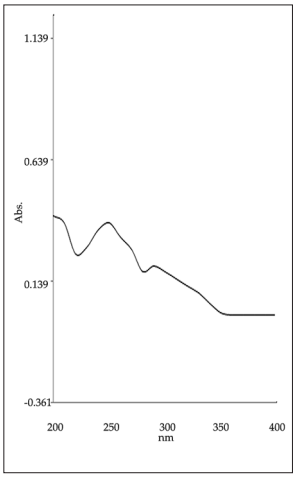

Figure 5: Zero order absorption spectra of ATV

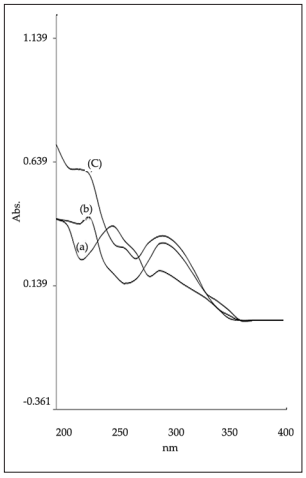

Figure 6: Zero order overlain spectra of (a) TELM, (b) ATV and (c) binary mixture of TELM and ATV

RESULTS AND DISCUSSION

The aim of this work is to establish and validate simple, sensitive, and accurate spectrophotometric method

according to ICH guidelines[17] with satisfactory precision and accuracy.

Linearity and sensitivity

The linearity of methods was evaluated by analyzing six concentrations of each drug and each concentration was repeated three times. Linear regression equation was obtained over the concentration ranges. Table 1 reveals the correlation coefficients along with standard deviation of slope (Sb) and that of intercept (Sa). The detection and quantitation limits were calculated based on standard deviation of response and slope. The detection and quantification limits obtained for TELM and ATV for derivative, absorbance ratio and multicomponent mode methods were tabulated.

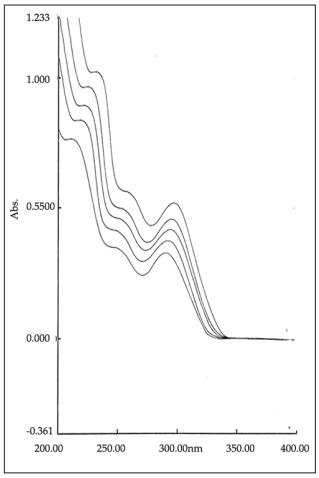

Figure 7: Overlain spectra of binary mixtures of TELM and ATV in multicomponent mode

Accuracy

Accuracy was assured by standard addition technique, performed by addition of known amounts of pure TELM and ATV to known concentrations of sample solution. The resulting mixtures were assayed in triplicate and results obtained were compared with expected results. The good recoveries as revealed in Table 2 indicate accuracy of the proposed methods.

Precision

Precision was ascertained by triplicate estimation of standard drugs on same day (intraday) and on three consecutive days (interday). The percentage relative standard deviation reveals good precision [Table 3].

Assay of tablet formulation

The results of analysis of tablet formulation (labeled to contain TELM 40 mg and ATV 10 mg) for three methods are shown in Table 4. The standard deviation

Table 1: Optical characteristics obtained for TELM and ATV by first derivative, Q-analysis and multicomponent method

Parameters	First derivative (D^1)		Q-analysis		Multicomponent mode	
	TELM	ATV	TELM	ATV	TELM	ATV
Measurement wavelength (nm)	272	223	296 (λ_{max}) and 280.9 (λ_{iso})		296	246.9
Range of linearity (µg/mL)	5–40	4–32	5–30	2–24	5–30	2–24
Regression equation	y=0.001x+0.003	y=0.002x+0.003	y=0.073x+0.009	y=0.041x-0.003	y=0.086x+0.006	y=0.0373x+0.004
S_b	0.003	0.00002	0.00051	0.0029	0.0015	0.00071
S_a	0.0012	0.0032	0.00021	0.0036	0.0004	0.0041
Correlation coefficient (r^2)	0.9971	0.9939	0.9997	0.9998	0.9983	0.9991
LOD (µg/ml)	0.40	0.37	0.30	0.13	0.35	0.19
LOQ (µg/ml)	2.12	2.07	2.71	1.81	2.65	1.76
Regression coefficient (r)	0.994	0.986	0.999	0.999	0.973	0.989

LOD=3.3×SD/slope; LOQ=10×SD/slope; S_a=Standard deviation of intercept of regression line; S_b=Standard deviation of slope of regression line

Table 2: Results of recovery study

Drug	Amount taken (µg/ml)	Amount added (µg/ml)	Amount recovered±SD*(µg/ml)	% RSD	Amount recovered±SD *(µg/ml)	% RSD	Amount recovered±SD *(µg/ml)	% RSD
			Method I		Method II		Method III	
TELM	20	16	36.02±0.032	0.088	35.92±0.028	0.077	36.05±0.051	0.14
		20	40.04±0.036	.090	39.90±0.010	0.025	40.12±0.038	0.09
		24	43.94±0.021	0.048	42.91±0.023	0.054	44.20±0.043	0.10
ATV	5	4	09.03±0.007	0.078	08.93±0.017	0.19	08.95±0.016	0.18
		5	10.04±0.011	0.108	09.95±0.03	0.30	09.95±0.024	0.24
		6	10.95±0.013	0.0118	10.90±0.013	0.12	11.02±0.014	0.13

Method I=First order derivative; Method II=Q-analysis method; Method III=Multicomponent mode, *Mean of three determinations

Table 3: Results of intraday and interday precision

Method	Precision	Amount taken (µg/ml)		% Mean*		% RSD	
		TELM	ATV	TELM	ATV	TELM	ATV
I	Intraday	20	5	100.23	101.57	0.091	0.112
	Interday	20	5	102.54	99.83	0.43	0.711
II	Intraday	20	5	101.10	98.47	0.073	0.091
	Interday	20	5	102.14	98.68	0.56	0.362
II	Intraday	20	5	101.03	99.67	0.25	0.301
	Interday	20	5	100.86	101.61	0.83	0.652

Method I=First order derivative; Method II=Q-analysis method; Method III=Multicomponent mode. *Mean of three determinations

Table 4: Results of tablet analysis

Parameters	Method I		Method II		Method III	
	TELM	ATV	TELM	ATV	TELM	ATV
Label claim (mg per tablet)	40	10	40	10	40	10
Drug content %±SD*	100.25±0.13	98.30±0.02	97.23±0.32	98.45±0.05	101.24±0.34	99.37±0.01
% RSD	0.32	0.21	0.81	0.51	0.84	0.10

Method I=First order derivative; Method II=Q-analysis method; Method III=Multicomponent mode. *Mean of five determinations

of five replicate analysis for all three methods were found to be <1. The assay values indicate that interference of excipients matrix is insignificant in the estimation of TELM and ATV by proposed methods.

CONCLUSION

The developed methods were found to be precise and accurate. The methods can be used for routine simultaneous spectrophotometric analysis of TELM and ATV in pharmaceutical preparations. Moreover, the developed methods have the advantages of simplicity, convenience and quantification of TELM and ATV for assay of their dosage form.

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