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Analytical Method Development and Validation for the Simultaneous Estimation of Telmisartan and Atorvastatin in Bulk and Tablet Dosage Form

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ABSTRACT

The current investigation was intended to improve the assay strategy for concurrent estimation of telmisartan and atorvastatin by utilizing instrument high performance liquid chromatography (HPLC), mobile phase of methanol:water, and 250 nm detection wavelength. The retention times were established to be 2.4 minutes for telmisartan and 3 minutes for atorvastatin. The analytical technique for both the drugs showed linearity over the range of 20 to 80 ppm of the target concentration. The recuperation was seen as 99.9% for both drugs. Both system framework and strategy precision were seen as precise and well inside the range. The detection limit of 0.05 for telmisartan and 0.019 for atorvastatin was found. The planned method was found to be simple, explicit, specific, linear, and rugged. Hence, it can be utilized for routine examination of telmisartan and atorvastatin in mass bulk and pharmaceutical formulations.

Keywords: Atorvastatin, Method development, Reversed-Phase High Performance Liquid Chromatography (RP-HPLC), Telmisartan, Validation.

1. INTRODUCTION

Telmisartan ($C_{33}H_{30}N_4O_2$) chemically known as (2-(4-{[4-methyl-6-(1-methyl-1H-1, 3-benzodiazol-2-yl)-2-propyl-1H-1, 3-benzodiazol-1-yl] methyl}phenyl)benzoic acid), Figure 1.[1] It is a vasodilator and angiotensin II receptor antagonist, utilized in the treatment of hypertension. Telmisartan reversibly and specifically binds to the angiotensin II AT_1-receptor in vascular smooth muscle and the adrenal gland and impedes the angiotensin II association. Telmisartan blocks the effect of angiotensin II, which causes a reduction in systemic vascular resistance. It does not restrain the action of angiotensin-converting enzyme, ion channels, or other hormone receptors. Research also suggested that telmisartan is a partial agonist of antidiabetic drugs target, PPARγ, this recommends that telmisartan can develop carbohydrate and lipid metabolism, and control resistance of insulin without causing the side effects related with full PPARγ activators.[2]

Atorvastatin ($C_{33}H_{34}FN_2O_5$) chemically is 7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoate, Figure 2.[3] Atorvastatin belongs to the class of statins, which is utilized for bringing down the cholesterol levels. It is a competitive inhibitor of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase. HMG-CoA reductase is the rate-determining enzyme in the biosynthesis of

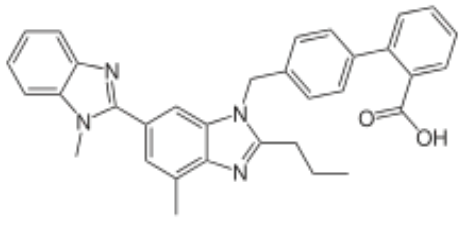

Figure 1: Telmisartan

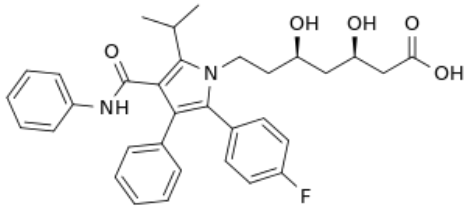

Figure 2: Atorvastatin

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cholesterol, which accelerates the transfer of HMG-CoA to mevalonate, principally in the liver.[4]

2. MATERIALS AND METHODS

2.1. Chemicals and Reagents

Telmisartan and atorvastatin were received as gift samples. HPLC grade methanol, acetonitrile, and purified KH_2PO_4 were procured from National Chemical Limited. The water of HPLC grade was used from the Milli-QRO system.

2.2. Instrumentation

HPLC-Waters (Model No. 2690/5 with series compact system), inertsil Octadecylsilyl (ODS) C18 column, ultrasonicator electronic weighing balance was used.

2.3. Buffer and Mobile Phase Preparation

2.3.1. *Mobile Phase*

The mobile phase in the present study used was methanol and water in the ratio of 50:50 v/v, after complete removal of foreign matters and gas.

2.3.2. *Buffer Preparation*

Dissolve 6.8 grams of KH_2PO_4 (20 mm) in 1,000 mL of HPLC grade water and sonicated for 20 minutes. Filter it with 0.45 µ size filter paper.

2.4. Standard and Sample Solution Preparation

2.4.1. *Preparation of Stock Solution*

10 mg of accurately weighed telmisartan and atorvastatin was dissolved completely in 10 mL of mobile phase, which was taken in two 10 mL of different volumetric flasks. This mixture was sonicated at 1,000 ppm for 20 minutes. 1 mL from each solution was taken and diluted with mobile phase to 10 mL.

Table 1: Optimized chromatographic conditions

Parameters	*Method*
Column	Inertsil-ODS C18 column
Mobile phase	Methanol and water in the ratio of 50:50 v/v
Flow rate (mL/min)	1 mL/min
Run time (minutes)	6 min
Temperature of column (°C)	Ambient
Injection loop volume (µL)	20 µL
Detection wavelength (nm)	250 nm
Drug RT (min)	2.4 min for telmisartan and 3 min for atorvastatin

2.4.2. *Preparation of Standard Solution (Reference Solution)*

10 mg of accurately weighed telmisartan and atorvastatin were dissolved in the mobile phase in a 100 mL volumetric flask. The final standard solution was prepared into a 100 mL volumetric flask by diluting 40 mL of above prepared solutions with methanol.

2.4.3. *Preparation of the Telmisartan and Atorvastatin Sample Solution*

Tablet powders of 2 mg telmisartan and 40 mg of atorvastatin were accurately weighed and taken into a 10 mL volumetric flask. Diluent (2 mL) was added and sonicated for completely dissolving the mixture. The final volume was prepared with the same solvent (stock solution) up to the mark. Additionally, 10 mL of the above stock solution was pipetted into a 100 mL volumetric flask, and diluted with diluent up to the mark.[5-8]

2.5. Optimized Chromatographic Conditions

The optimized chromatographic conditions are presented in Table 1.

2.6. Validation of Method

The present analytical method was validated as per the guidelines of ICH with reference to various factors like linearity, specificity, precision, accuracy, the limit of detection (LOD), the limit of quantitation (LOQ), and robustness.[9-11]

3. RESULTS AND DISCUSSION

3.1. System Suitability

The separation and peak shape were observed to be excellent. Hence, reduction in the retention times of peaks in not required. Therefore, this was considered as the final method (Figures 3 and 4).

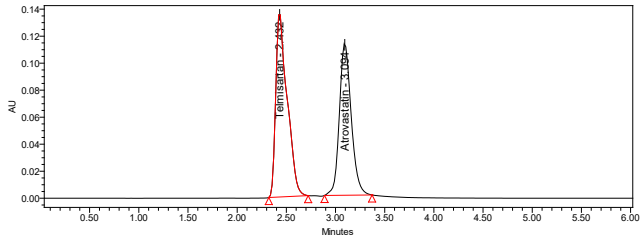

Figure 3: Chromatogram of standard

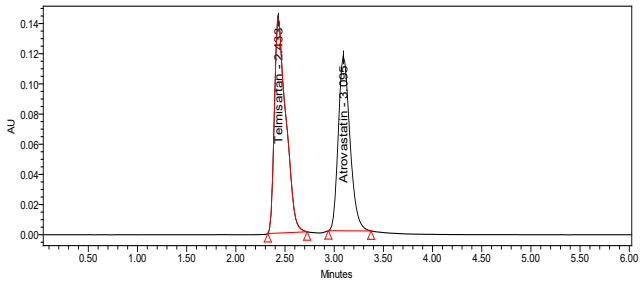

Figure 4: Chromatogram of sample

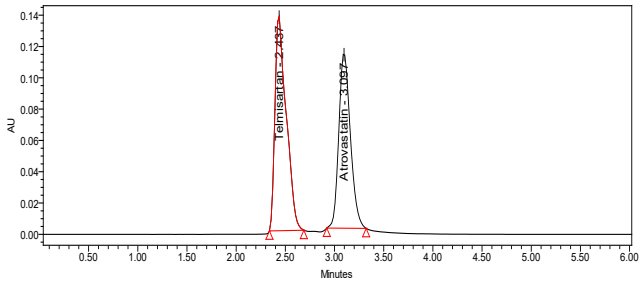

Figure 5: Chromatogram of standard

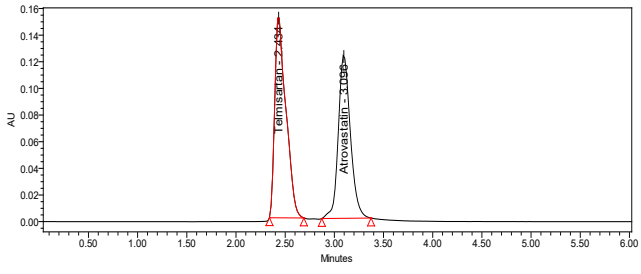

Figure 6: Chromatogram of sample

3.2. Validation Parameters

3.2.1. *Specificity*

The specificity of system suitability was performed to conclude if there is any obstruction due to impurities in the retention time of an analytical peak. The method of specificity was carried out by infusing blank. The chromatograms of the standard sample and test sample were found to be identical with the same retention time (RT of 2.4 minutes for telmisartan and 3 minutes for atorvastatin), Figures 5 and 6.

3.2.2. *Linearity*

With working standards of telmisartan and atorvastatin, a sequence of solutions was prepared at different concentrations ranging from 20 to 80 ppm of the target concentration. The peak area obtained for the solution was measured at levels 1 and 6 for the six times and levels 2 to 5 for two times. The linear presentation of this system was given graphically. The outcomes were presented in Tables 2 and 3, and Figures 7 and 8.

3.2.3. *Accuracy (Recovery)*

The assay of telmisartan and atorvastatin was carried out with equal concentrations in triplicate according to the test procedure for each spike level to obtain the concentration of the drugs equivalent to 50, 100, and 150% of the labeled amount. The average percentage recovery of telmisartan and atorvastatin were calculated.

Table 2: Linearity of telmisartan

Concentration (ppm)	*Average area*	*Statistical analysis*	
0	0	Slope	5407
20	108,479	y-intercept	84.36
30	162,204	Correlation coefficient	1
40	216,405		
50	270,321		
60	324,713	-	-
70	378,640		
80	432,684		

Table 3: Linearity of atorvastatin

Concentration (ppm)	*Average area*	*Statistical analysis*	
0	0	Slope	24,502
20	490,525	y-intercept	262.4
30	735,189	Correlation coefficient	1
40	980,421		
50	1,225,471		
60	1,470,759	-	-
70	1,715,409		
80	1,960,011		

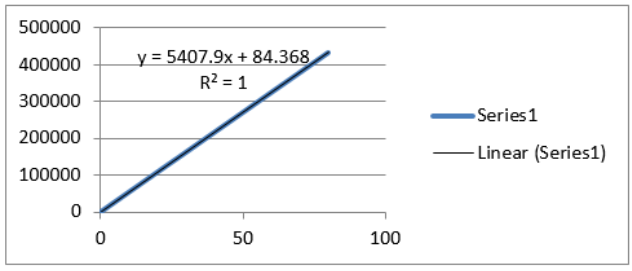

Figure 7: Linearity plot of telmisartan

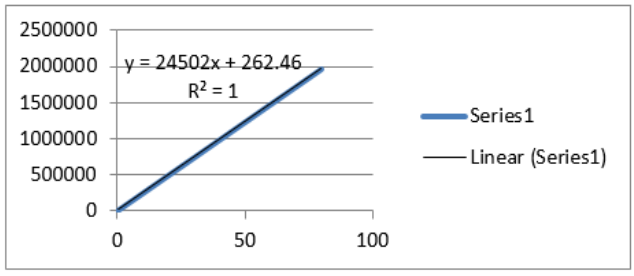

Figure 8: Linearity plot of atorvastatin

Table 4: Accuracy results for telmisartan

% concentration (at specification level)	*Amount added (mg)*	*Amount found (mg)*	*% recovery*	*Mean recovery*
50	20	19.97	99.85	
100	40	39.96	99.9	99.91%
150	60	60	100	

Table 5: Accuracy results for atorvastatin

% concentration (at specification level)	*Amount added (mg)*	*Amount found (mg)*	*% recovery*	*Mean recovery*
50	20	19.99	99.95	
100	40	39.98	99.95	100.06%
150	60	60.02	100.03	

Table 6: Precision repeatability for telmisartan and atorvastatin

Drug name	*Con-centration*	*Injection*	*Peak area*	*% assay*	*Drug name*	*Con-centration*	*Injection*	*Peak area*	*% assay*
Telmisartan	40 ppm	1	216,848	100.1	Atorvastatin	40 ppm	1	980,203	99.9
		2	216,572	100			2	980,186	99.9
		3	216,455	100			3	980,536	100
		4	216,810	100.1			4	980,857	100
		5	216,687	100.1			5	980,806	100
		6	216,848	100.2			6	980,514	99.96
	Mean		216,703	100		Mean		980,517	99.96
	Std		114.7386	0.0752		Std		319.2324	0.054772
	% RSD		0.07	0.07		% RSD		0.03	0.05

Table 7: Intermediate precision for telmisartan and atorvastatin

Drug name	*Con-centration*	*Injection*	*Peak area*	*% assay*	*Drug name*	*Con-centration*	*Injection*	*Peak area*	*% assay*
Telmisartan	40 ppm	1	216,415	100	Atorvastatin	40 ppm	1	980,536	100
		2	216,455	100			2	980,391	100
		3	216,351	99.9			3	980,857	100.1
		4	216,810	100.1			4	980,314	99.9
		5	216,305	99.8			5	980,806	100.1
		6	216,687	100			6	980,023	99.98
	Mean		216,503	99.96		Mean		980,487	99.98
	Std		200.2283	0.103		Std		314.80124	0.116
	% RSD		0.09	0.1		% RSD		0.03	0.11

$$\%\ recovery = \frac{\text{Amount } found}{\text{Amount } added} \times 100$$

The outcomes of the recovery method indicated that the test method has an adequate degree of accuracy. Accuracy results are presented in Tables 4 and 5.

3.2.4. *Precision*

The selected test method showed a precision of 0.07 and 0.3, indicating the method was precise. Individual % assays and % relative standard deviation (RSD) of the assay are also observed to be in limits and passes the intermediate precision; results are presented in Tables 6 and 7.

Table 8: System suitability for telmisartan

Injection	RT	Peak area	USP plate count	USP tailing
1	2.437	216,415	9,704.196947	1.192463
2	2.435	216,455	9,719.025949	1.193302
3	2.433	216,351	9,750.55575	1.23804
4	2.432	216,810	9,837.749192	1.213925
5	2.437	216,305	9,768.539874	1.264769
Mean	2.438	216,467	9,756.014	1.2205
SD	0.00228	200.123	-	-
% RSD	0.093	0.09	-	-

Table 9: System suitability for atorvastatin

Injection	RT	Peak area	USP plate count	USP tailing
1	3.09	980,536	10,942.894891	1.654151
2	3.098	980,391	10,997.527815	1.618302
3	3.095	980,857	10,912.595477	1.629762
4	3.094	980,314	10,945.938838	1.624684
5	3.097	980,806	10,936.014865	1.609883
Mean	3.0948	980,580	10,946.99	1.627356
SD	0.0031	243.009	-	-
% RSD	0.1	0.02	-	-

3.2.5. *System Suitability*

By using telmisartan and atorvastatin working standards, a standard solution was prepared according to the test method. This solution was then injected five times into the HPLC system. The parameters of system suitability were estimated from standard chromatograms by determining the % RSD from 5 replicate infusions for telmisartan and atorvastatin. The % RSD for peak areas and retention times were found to be in acceptable limits; results are presented in Tables 8 and 9.

3.2.6. *Limit of Detection and Quantitation (LOD and LOQ)*

From the data of linearity, the limit of detection and quantitation was calculated. The formula used for calculation is as follows,

$$LOD = \frac{3\sigma}{S}$$

Where σ = response standard deviation and S = calibration curve slope.

Limit of Quantification (LOQ)

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

Where σ = response standard deviation and S = calibration curve slope.

The LOD and LOQ were calculated from the plot of linearity. The detection limit was found to be 0.05 for telmisartan and 0.019 for atorvastatin.

4. CONCLUSION

In the present study, a novel technique was set up for the simultaneous estimation of telmisartan and atorvastatin by the method of RP-HPLC. The chromatographic circumstances were effectively exploited for the partition of telmisartan and atorvastatin by employing inertsil ODS C18 column, 1 mL/min flow rate, methanol and water as mobile phase, and 250 nm detection wavelength. The linearity, recovery studies, and precision were reported to be in the acceptable range. The systemic analytical method has passed the robustness and ruggedness assessments. In the two cases, the relative standard deviation was well palatable. For the routine analytical reason, it is alluring to set up methods that are proficient for examining a tremendous number of samples in a less time period without any prior separation step and with efficient precision, robustness, and accuracy. HPLC method and the spectrophotometric technique produce an enormous amount of valued quality data, which serves a profoundly incredible and convenient analytical tool.

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