Research Article

Stability Indicating Simultaneous Validation of Telmisartan and Cilnidipine with Forced Degradation Behavior Study by RP-HPLC in Tablet Dosage Form

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A simple, precise, and accurate RP-HPLC method has been developed and validated for the simultaneous assay of Telmisartan and Cilnidipine in tablets. Isocratic RP-HPLC method was developed on Waters C18 250 × 4.6 mm, 5 μm column using mobile phase as acetonitrile (ACN): buffer pH 3.0 with orthophosphoric acid (68 : 32) at a flow rate of 1.0 mL/min and the detection was carried out at 245 nm using photodiode array detector. Forced degradation study was carried out by oxidation, hydrolysis, photolysis, and heating the drug. The method was validated for specificity, linearity, precision, accuracy, robustness, and solution stability. The method was found to be linear in the concentration range of 40–160 μg/mL with correlation coefficient of 0.9990 for Telmisartan and 10–40 μg/mL with correlation coefficient of 0.9989 for Cilnidipine. Degradation products produced as a result of stress studies did not interfere with the detection of agomelatine; therefore, the assay can be considered to be stability indicating.

1. Introduction

Telmisartan is chemically nominated as 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazole]-1'-yl) methyl] [1,1'-biphenyl]-2-carboxylic acid (Figure 1). Its molecular formula is $C_{33}H_{30}N_4O_2$ and molecular weight is 514.62. It is a diabetes angiotensin receptor blocker that shows high affinity for the angiotensin II type 1 (AT1) receptors, has a long duration of action, and has the longest half-life of any angiotensin II receptor blocker (ARB) [1]. In clinical studies, Telmisartan shows comparable antihypertensive activity to other major antihypertensive classes, such as angiotensin converting enzyme (ACE) inhibitors, beta-blockers, and calcium antagonists [2].

Cilnidipine is chemically nominated as 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridine carboxylic acid 2-methoxyethyl(2E)-3-phenyl-propenyl ester (Figure 2). It is a dual blocker of L-type voltage-gated calcium channels in vascular smooth muscle and N-type calcium channels in sympathetic nerve terminals that supply blood vessels [3].

The parent drug stability test guideline Q1A (R2) issued by the International Conference on Harmonization (ICH)

suggests that stress testing is an essential part of development strategy and is carried out under more severe condition than accelerated conditions. These studies provide information to establish its inherent stability characteristics, leading to identification of degradation products and hence supporting the suitability of the proposed analytical methods. [4–6]. According to ICH guidelines stress testing should include the effect of temperature, light, oxidizing agents and susceptibility across a wide range of pH values and separation of drugs from degradation products [7]. It is also suggested that analysis of stability sample should be done by using validated stability testing methods.

There are many reported methods for analysis of Telmisartan [8–13] and Cilnidipine [3, 14–16] either alone or in combination with other drugs in pharmaceutical dosage forms or individually in biological fluids. Simultaneous RP-HPLC and HPTLC estimation of Telmisartan and Cilnidipine in combined tablet dosage form has been reported [17, 18]. To our knowledge there has been no stability indicating RP-HPLC method reported for Telmisartan and Cilnidipine combination in which ICH recommended that stress

FIGURE 1: Chemical structure of Telmisartan.

FIGURE 2: Chemical structure of Cilnidipine.

conditions be applied. Therefore, the stability indicating method was developed by applying different stress conditions like acidic, alkali, H_2O_2 , thermal, and photodegradation.

2. Experimental

2.1. Instrumentation. The chromatographic system used to perform development and validation of this assay method was comprised of a LC-10ATvp binary pump, a SPD-M10Avp photodiode array detector, and a Rheodyne manual injector model 7725i with 20 μ L loop (Shimadzu, Kyoto, Japan) connected to a multi-instrument data acquisition and data processing system (LC solution, Shimadzu).

2.2. Reagents and Reference Substance. Telmisartan and Cilnidipine standards were provided by Unique Chemicals, Panoli, India, and CPL Chemicals, Ankleshvar, India, respectively. Cilacar T tablets containing 40 mg Telmisartan and 10 mg Cilnidipine were obtained from market. HPLC grade ACN was obtained from Spectrochem Pvt. Ltd., Mumbai, India. HPLC grade water was produced in-house by using Milli Q (Millipore, Milford, USA) system. Membrane filters of 0.45 μ m (Millipore) were used. Analytical grade sodium phosphate monobasic dihydrate was obtained from Sisco Research Laboratories, Mumbai, India. Hydrochloric acid, glacial acetic acid, sodium hydroxide pellets, and 30% v/v hydrogen peroxide solution were obtained from Ranbaxy Fine Chemicals, New Delhi, India.

2.3. Chromatographic Conditions. Chromatographic analysis was performed on Waters C 18 (250 mm $\times$ 4.6 mm i.d., 5 μ m particle size) column at ambient temperature. The mobile phase consisted of ACN: 0.01 M sodium phosphates

monobasic dehydrate buffer pH 3.0 with phosphoric acid (68 : 32, v/v). Buffer solution was filtered through a 0.45 μ m nylon membrane (Millipore Pvt. Ltd. Bangalore, India) and mobile phase was degassed in an ultrasonic bath (Spincotech Pvt. Ltd., Mumbai). The flow rate of the mobile phase was adjusted to 1.0 mL/min and the injection volume was 20 μ L. Detection was performed at 245 nm.

2.4. Standard Preparation. Standard solution containing Telmisartan (100 μ g/mL) and Cilnidipine (25 μ g/mL) was prepared by dissolving accurately about 100.0 mg Telmisartan and 25.0 mg Cilnidipine in 100 mL volumetric flask by diluent (methanol) (stock standard solution). 10 mL of stock solution was pipetted out into 100 mL volumetric flask and diluted up to mark with diluent to get concentration 100 μ g/mL for Telmisartan and 25 μ g/mL for Cilnidipine.

2.5. Test Preparation. Twenty tablets were weighed and the average weight of tablet was determined. From these, five tablets were weighed and transferred into a 500 mL volumetric flask. About 50 mL diluent was added and sonicated for a minimum of 30 min. with intermittent shaking.

Then content was brought back to room temperature and diluted to volume with diluent. The sample was filtered through 0.45 μ m nylon syringe filter. 25 mL of filtrate stock solution was pipetted out into 100 mL volumetric flask and diluted up to mark with diluent. The concentration obtained was 100 μ g/mL of Telmisartan and 25 μ g/mL of Cilnidipine.

2.6. Degradation Study. The degradation samples were prepared by transferring powdered tablets, which had been equivalent to 40.0 mg Telmisartan and 10.0 mg Cilnidipine, into a 250 mL round bottomed flask. Then drug content was employed for acidic, alkaline, and oxidant media and also for thermal and photolytic stress conditions. After the degradation treatments were completed, the stress content solutions were allowed to equilibrate to room temperature and diluted with diluent to attain 100 μ g/mL Telmisartan and 25 μ g/mL Cilnidipine concentration. Specific degradation conditions were described as follows.

2.7. Acidic Degradation Condition. Acidic degradation study was performed by heating the drug content in 1 N HCl at 60°C for 30 min and mixture was neutralized.

2.8. Alkali Degradation Condition. Alkaline degradation study was performed by ambient temperature in 1 N NaOH for 30 min and mixture was neutralized.

2.9. Oxidative Degradation Condition. Oxidation degradation study was performed by heating the drug content in 30% v/v H_2O_2 at 80°C for 1 hour. Here 80°C temperature was used because at 60°C degradation was not obtained.

2.10. Thermal Degradation Condition. Thermal degradation was performed by exposing solid drug to dry heat of 80°C

in a conventional oven for 72 hr. Here 80°C temperature was used because at 60°C degradation was not obtained.

2.11. Photolytic Degradation Condition. Photolytic degradation study was performed by exposing the drug content in UV-light for 72 hr.

3. Method Validation

3.1. Specificity Study. The specificity of the method was determined by checking the interference of placebo with analyte and the proposed method was eluted by checking the peak purity of Telmisartan and Cilnidipine during the force degradation study. The peak purity of the Telmisartan and Cilnidipine was found to be satisfactory (0.9999) and (0.9998) under different stress conditions. There was no interference of any peak of degradation product with drug peak.

3.2. Linearity. Linearity test solutions for the assay method were prepared at seven concentration levels from 40 to 160% of assay analyte concentration (40, 60, 80, 100, 120, 140, and 160 µg/mL) with correlation coefficient of 0.9990 for telmisartan and (10, 15, 20, 25, 30, 35, and 40 µg/mL) with correlation coefficient of 0.9989 for Cilnidipine. The peak areas versus concentration data were evaluated by linear regression analysis.

3.3. LOD and LOQ. The limit of detection and limit of quantification were evaluated by serial dilutions of telmisartan and Cilnidipine stock solution in order to obtain signal-to-noise ratio of 3:1 for LOD and 10:1 for LOQ.

3.4. Precision. The precision of the assay method was evaluated in terms of repeatability by carrying out six independent assays of telmisartan and Cilnidipine test sample preparation and calculated the % RSD of assay (intraday). Intermediate precision of the method was checked by performing same procedure on a different day (interday) by another person under experimental condition.

3.5. Accuracy. An accuracy study was performed by adding known amounts of Telmisartan and Cilnidipine to the placebo preparation. The actual and measured concentrations were compared. Recovery of the method was evaluated at three different concentration levels (corresponding to 50, 100, and 150% of test preparation concentration). For each concentration level, three sets were prepared and injected in duplicate.

3.6. Robustness. The robustness of study was carried out to evaluate the influence of small but deliberate variations on the chromatographic conditions. The factors chosen for this study were the flow rate (± 0.1 mL/min), mobile phase composition [ACN-buffer (70:30 and 66:34, v/v)], and using different lot of LC column.

3.7. Solution Stability. The stability study of solution for test preparation was carried out. The solution was stored at

FIGURE 3: Chromatogram of standard preparation.

ambient temperature 2–5°C and tested at intervals of 12, 24, 36, and 48 hr. The responses for the aged solution were evaluated using a freshly prepared standard solution.

3.8. Result and Discussion. An analytical method based on LC with UV detection was developed and validated for assay and determination of Telmisartan and Cilnidipine in tablet dosage forms. The analytical conditions were selected after testing the different parameters such as diluents, buffer, buffer concentration, organic solvent for mobile phase and mobile phase composition, and other chromatographic conditions. Our preliminary trials using different compositions of mobile phases, consisting of water with methanol or acetonitrile, did not give good peak shape. Then different pH of water was used with methanol and acetonitrile, but good peak shape was not obtained. By keeping mobile phase composition CAN-0.01 M sodium phosphate monobasic dehydrate buffer (68:32, v/v) pH 3, best peak shape was obtained. For the selection of organic constituent of mobile phase, acetonitrile was chosen to reduce the longer retention time and to attain good peak shape. A detection wavelength of 245 nm was selected after scanning the standard solution over the range 190–370 nm by use of the PDA detector. Detection at 245 nm resulted in good response and good linearity. Chromatogram of standard preparation is represented in Figure 3.

The drug substance was easily extracted from the pharmaceutical dosage form using methanol. The tablet dispersed readily in water and the drug substance was freely soluble in methanol. Solutions of standard and test preparation were found to be stable in methanol which was used as a diluent.

After development of the analytical method, it was validated in accordance with ICH and USP guidelines. This furnished evidence that the method was suitable for its intended purpose. The intensive approach described in this paper was used to develop and validate a liquid chromatographic analytical method that can be used for assay validation of telmisartan and Cilnidipine in a pharmaceutical dosage form. Degradation product produced as a result of stress did not interfere with detection of Telmisartan and Cilnidipine and the assay method can thus be regarded as stability indicating.

The specificity of the method was evaluated by checking the interference of placebo with analyte and the proposed method was evaluated by checking the peak purity of Telmisartan and Cilnidipine during the force degradation study. There was no interference of any peak of degradation product with drug peak.

FIGURE 4: Chromatogram of alkali forced degradation study.

FIGURE 5: Linearity curve for Telmisartan.

Major degradation was found in alkali condition that product was degraded up to 5.74% for Telmisartan where two degradation peaks were found at 3.460 and 5.786, while for Cilnidipine the product was degraded up to 32.99% at 12.096 min. (Figure 4). There was no degradation found in acid, 3% H_2O_2 , 30% H_2O_2 , thermal and photo degradation for both Telmisartan and Cilnidipine.

To determine linearity a calibration graph was obtained by plotting Telmisartan and Cilnidipine concentration (mg/mL) against peak area. Linearity was good in the concentration range 40–160 µg/mL for Telmisartan (Figure 5) and 10–40 µg/mL for Cilnidipine (Figure 6). The response of the drug was found to be linear. The regression equation for Telmisartan was $y = 69,963,612.50x + 121,403.61$ with correlation coefficient 0.9990 and for Cilnidipine was $y = 100,294,307.14 + 21,397.04$ with correlation coefficient 0.9989 where x is the concentration in µg/mL and y is the peak area in absorbance units (AU).

The LOD values for telmisartan and Cilnidipine were found to be 0.01 ppm and 0.09 ppm, respectively. The LOQ values for telmisartan and Cilnidipine were 0.06 ppm and 0.4 ppm.

For assay of Telmisartan ($n = 6$), RSD of system precision was 0.20% on the same day (intraday) and 0.36% on different days (interday). The mean values of % assay and % RSD for method precision (repeatability) were 100.35% and 0.43%, respectively, for assay on same day (intraday), while 99.72% and 0.56%, respectively, for assay on different days (interday).

For assay of Cilnidipine ($n = 6$), RSD of system precision was 0.14% on the same day (intraday) and 0.22% on different days (interday). The mean values of % assay and % RSD

FIGURE 6: Linearity curve for Cilnidipine.

for method precision (repeatability) were 99.83% and 0.86%, respectively, for assay on the same day (intraday), while 99.93% and 0.45%, respectively, for assay on different days (interday).

Intermediate precision was established by determining the overall (intraday and interday) method precision. For intermediate precision ($n = 12$), overall % assay and % RSD value was 100.04% and 0.58%, respectively, for Telmisartan, while 99.88% and 0.66% for Cilnidipine. The precise result for content uniformity was indicative of uniform distribution of the drug in the tablets without significant variation; this is in accordance with the USP, which stipulates acceptance limits for drug content uniformity and RSD as 85–115% and <6%, respectively [19].

The accuracy of the method was assessed by determination of recovery for three concentrations covering the range of the method. Known amounts (50, 100, and 150 µg/mL) for Telmisartan and (12.5, 25.0, and 37.5 µg/mL) for Cilnidipine were added to a placebo preparation and the amount of Telmisartan and Cilnidipine recovered, in the presence of placebo interface, was calculated. The mean recovery of Telmisartan was 98.37%, 98.09%, and 99.79%, respectively, and the mean recovery of Cilnidipine was 99.68%, 98.89%, and 99.52%, respectively (Table 1).

The robustness of the method was assessed by assaying test solutions under different analytical conditions deliberately changed from the original conditions. For each different analytical condition the standard solution and test solution were prepared separately. The result obtained from assay of the test solution was not affected by varying the conditions and was in accordance with the true value. System suitability data were also found to be satisfactory during variation of the analytical conditions (Table 2). The analytical method therefore remains unaffected by slight but deliberate changes in the analytical conditions.

During the study of the stability of stored solutions of standards and test preparations for assay determination the solutions were found to be stable for up to 48 hr. Assay values obtained after 48 hr were statistically identical with the initial value without measurable loss (Table 3).

Before each measurement of validation data a system suitability test was performed by measurement of general characteristics such as peak asymmetry, number of theoretical plates, and RSD (%) of peak area observed for

TABLE 1: Evaluation data of accuracy study.

	Level (%)	Theoretical concentration ^a (mg/mL)	Observed concentration ^a (mg/mL)	% Recovery	% RSD
Telmisartan	50	0.04998	0.04917	98.37	1.68
	100	0.09995	0.09804	98.09	0.58
	150	0.14993	0.14963	99.79	1.20
Cilnidipine	50	0.01253	0.01246	99.69	0.49
	100	0.02505	0.02477	98.89	0.13
	150	0.03752	0.03734	99.52	0.15

^aEach value corresponds to the mean of six determinations.

TABLE 2: Evaluation data of robustness study.

Robust conditions	% Assay	System suitability parameters	
		Theoretical plates	Asymmetry
Flow 0.9 mL/min.	100.31	3448	1.03
Flow 1.1 mL/min.	99.76	3372	0.98
Buffer-ACN (34 : 66, v/v)	99.77	3397	1.02
Buffer-ACN (30 : 70, v/v)	99.76	3362	1.07
Column change	100.37	3290	1.03

TABLE 3: Evaluation data of stability study.

Intervals	% Assay for test solution stored at 2–8°C		% Assay for test solution stored at ambient temperature	
	Telmisartan	Cilnidipine	Telmisartan	Cilnidipine
Initial	99.56	99.71	99.99	99.66
12 h	99.61	99.85	100.11	100.17
24 h	99.54	99.84	100.14	99.77
36 h	99.98	99.23	100.18	99.45
48 h	99.74	100.15	99.89	100.20

a standard solution. The values obtained were satisfactory and in accordance with in-house limits (Tables 4 and 5).

4. Conclusion

This LC method for simultaneous assay validation of Telmisartan and Cilnidipine in a tablet formulation was successfully developed and validated for its intended purpose. In this study, stability of Telmisartan and Cilnidipine in present dosage form was established through employment of ICH recommended stress condition. The developed procedure has been evaluated over the specificity, linearity, accuracy, precision, and robustness in order to ascertain the stability of the analytical method. It has been proved that it was specific, linear, precise, accurate, robust, and stability indicating. Hence, the method is recommended for routine quality control analysis and also stability sample analysis.

TABLE 4: Evaluation data of system suitability study for Telmisartan.

System suitability data	RSD (%)	Theoretical plates	Asymmetry
In-house limit	NMT ^b 2.0	NLT ^c 2000	NMT ^b 2.0
Specificity	1.02	3628	1.24
Linearity	0.53	3290	1.46
Precision	0.20	3799	1.34
Intermediate precision	0.36	3730	1.38
Accuracy	0.83	3528	1.29
Solution stability	0.16	3026	1.20
Robustness	0.71	3413	1.45

^bMeans not more than and ^cmeans not less than.

TABLE 5: Evaluation data of system suitability study for cilnidipine.

System suitability data	RSD (%)	Theoretical plates	Asymmetry
In-house limit	NMT ^b 2.0	NLT ^c 2000	NMT ^b 2.0
Specificity	0.26	10214	1.35
Linearity	0.69	9823	1.23
Precision	0.14	10195	1.29
Intermediate precision	0.22	10166	1.40
Accuracy	0.55	10081	1.38
Solution stability	0.29	10372	1.15
Robustness	0.62	10224	1.26

^bMeans not more than and ^cmeans not less than.

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