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Research Article

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

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ABSTRACT
A simple, précised and accurate RP-UPLC method has been developed and validated for the simultaneous assay of Telmisartan and Cilnidipine in tablets. Isocratic RP-UPLC method was developed on LC system of Waters Acquity UPLC with PDA detector onWater Acquity BEH C18, 2.1 x 100mm, 1.7µm column as stationary phase with binary gradient mode by using mobile phase as ACN: 0.01M sodium phosphates monobasic dehydrate buffer pH 3.0 with phosphoric acid (68:32, v/v), at a flow rate of 0.5 ml/min and the detection was carried out at 245 nm. 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 coefficients of 0.9996 for Telmisartan and 10-40 µg/ml with correlation coefficients of 0.9995 for Cilnidipine. Degradation products produced as a result of stress studies did not interfere with the detection of Telmisartan and Cilnidipine: therefore, the assay can be considered to be stability-indicating.

Keywords: Cilnidipine, Telmisartan, Stability-indicating, Method Validation, Degradation Behavior Study.

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 (Fig.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 angeotensin II type 1 (AT1) receptors, has a long duration of action and has the longest half-life of any angeotensin 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. 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 International Conference on Harmonization (ICH) suggests that stress testing is an essential part of development strategy and is carried out under more serve 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 as well as 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-UPLC method reported for Telmisartan and Cilnidipine combination in which ICH recommended stress conditions were applied. Therefore, the stability indicating method was developed by applying different stress conditions like acidic, alkali, H_2O_2, thermal and photo degradation.

Experimental

Instrumentation

The LC system of Waters Acquity UPLC with PDA was used for this entire study and chromatographic separation was achieved on Water Acquity BEH C18, 2.1 x 100mm, 1.7µm column as stationary phase with binary gradient mode.

Reagents and reference substance

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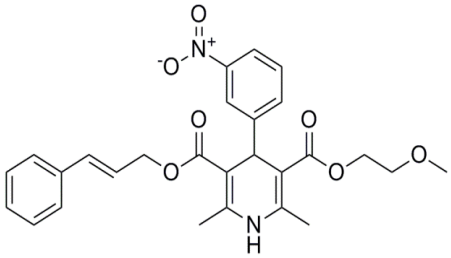

Figure 1: Chemical structure of Telmisartan

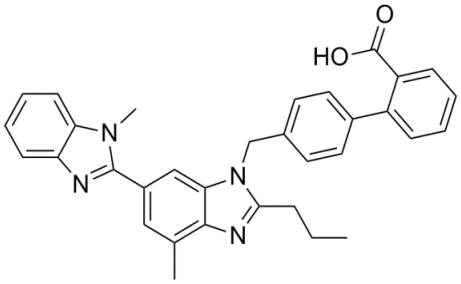

Figure 2: Chemical structure of Cilnidipine

Telmisartan and Cilnidipine standard were provided by Unique Chemicals, Panoli (India) and CPL Chemicals, Ankleshvar (India) respectively. Cilacar T tablets containing 40mg Telmisartan and 10mg Cilnidipine were obtained from market. HPLC grade ACN was obtained from Spectrochem Pvt. Ltd., Mumbai (India). UPLC grade water was produced in-house by using Milli Q (Millipore, Millford, USA) system. Membrane filters of 0.45µm (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).

Chromatographic conditions

Chromatographic analysis was performed on Waters Acquity BEH C18, 2.1 x 100mm, 1.7µm column. The mobile phase was consisted of ACN: 0.01M sodium phosphates monobasic dehydrate buffer pH 3.0 with phosphoric acid (68:32, v/v). The flow rate of the mobile phase was adjusted to 0.5 mL/min and the injection volume was 1 µl. Detection was performed at 245 nm.

Standard preparation

Standard solution containing Telmisartan (100µg/ml) and Cilnidipine (25µg/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). 10ml of stock solution was pipetted out into 100 ml volumetric flask and diluted up to mark with diluent to get concentration 100µg/ml for Telmisartan and 25µg/ml for Cilnidipine.

Test preparation

Twenty tablets were weighed and the average weight of tablet was determined. From these, five tablets were weighed and transfer into a 500 ml volumetric flask. About 50 ml diluent was added and sonicated for a minimum 30 min. with intermittent shaking. Then content was brought back to room temperature and diluted to volume with diluent. The sample was filtered through 0.45µm nylon syringe filter. 25 ml of filtrate stock solution was. pipetted out into 100 ml volumetric flask and dilute up to mark with diluent. The concentration obtained was 100 µg/ml of Telmisartan and 25µg/ml of Cilnidipine.

Degradation study

The degradation samples were prepared by transferring powdered tablets, equivalent to 40.0 mg Telmisartan and 10.0 mg Cilnidipine into a 250 ml around 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 µg/ ml Telmisartan and 25 µg/ ml Cilnidipine concentration. Specific degradation conditions were described as follows.

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.

Alkali degradation condition

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

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 temperatures used because at 60°C degradation was not obtained.

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 temperatures used because at 60°C degradation was not obtained.

Photolytic degradation condition

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

Method Validation

Specificity study

The specificity of the method was determined by checking the interference of placebo with analyte. The peak purity was found satisfactory under different stress condition for both Telmisartan and Cilnidipine. There was no interference of any peak of degradation product with drug peak.

Linearity

For linearity seven points calibration curve were obtained in a concentration range from 0.04-0.16 mg/ml for Telmisartan and 0.010-0.040 mg/ml for Cilnidipine. The response of the drug was found to be linear in the investigation concentration range and the linear regression equation for Telmisartan was y = 12,800,570.01x - 8,031.75with correlation coefficient 0.9996 (Figure 9) and for Cilnidipine was y = 20,094,521.30x - 6,693.40 with correlation coefficient 0.9995 (Figure 10). Where x is the concentration in mg/ml and y is the peak area in absorbance unit.

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.

Precision

Data obtained from precision experiments are given in Table 1 for intraday and inter-day precision study for both Telmisartan and Cilnidipine. The RSD values for intraday precision study and inter-day precision study was < 2.0 % for Telmisartan and Cilnidipine, which confirms that the method was precise.

Accuracy

Recovery of Telmisartan and Cilnidipine were determined at three different concentration levels. The mean recovery for Telmisartan was 99.20-100.03 % and for Cilnidipine was 98.11-99.46 % (Table 2). The results indicating that the method was accurate.

Robustness

The result of robustness study of the developed assay method was established in Table 4 and Table 5. The result shown that during all variance conditions, assay value of the test preparation solution was not affected and it was in accordance with that of actual. System suitability parameters were also found satisfactory; hence the analytical method would be concluded as robust.

Solution stability

The stability study of solution for test preparation was carried out. The solution was stored at ambient temperature and 2-5˚C and tested at interval of 12, 24, 36 and 48 hr. The responses for the aged solution were evaluated using a freshly prepared standard solution.

RESULTS AND DISCUSSION

Proper selection of the methods depends upon the nature of the sample (ionic or ionisable or neutral molecule), its molecular weight and solubility. Telmisartan and Cilnidipine are dissolved in polar solvent hence RP-UPLC was selected to estimate them. To develop a rugged and suitable UPLC method for the quantitative determination of Telmisartan and Cilnidipine, the analytical condition was 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 composition of mobile phases consisting of water with methanol or acetonitrile, did not give good peak shape. By using Buffer (0.01M sodium phosphates monobasic dehydrate buffer pH 3.0 with OPA): Acetonitrile (32: 68, v/v), 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. Chromatogram of standard preparation is represented in (Fig. 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 the method was suitable for its intended purpose. The intensive approach described in this manuscript 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. Major degradation was found in alkali condition that product was degraded up to 5.74 % for Telmisartan where, two degradation peaks found at 3.460 and 5.786 while, for Cilnidipine the product was degraded up to 32.99 % at 12.096min. (Fig.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. For linearity seven points calibration curve were obtained in a concentration range from 0.04-0.16 mg/ml for Telmisartan and 0.010-0.040 mg/ml for Cilnidipine. The response of the drug was found to be linear in the investigation concentration range and the linear regression equation for Telmisartan was y = 12,800,570.01x - 8,031.75with correlation coefficient 0.9996 (Figure 5) and for Cilnidipine was y = 20,094,521.30x - 6,693.40 with correlation coefficient 0.9995 (Figure 6). Where x is the concentration in mg/ml and y is the peak area in absorbance unit. For assay of Telmisartan (n=6), RSD of system precision was 1.15% on the same day (intra-day) and 0.38% on different days (inter-day). The mean values of % assay and % RSD for method precision (repeatability) were 99.81% and 0.66% respectively for assay on same day (intra-day) while,

Table 1: Evaluation data of accuracy study

	Level (%)	Theoretical concentration[a] (µg/ml)	Observed concentration[a] (µg/ml)	% Recovery	% RSD
Telmisartan	50	49.95	49.55	99.20	1.67
	100	100.04	100.07	100.03	0.07
	150	150.14	149.04	99.26	0.86
Cilnidipine	50	12.51	12.27	98.11	0.36
	100	25.02	24.89	99.46	1.23
	150	37.34	37.01	99.12	0.69

[a]Each value corresponds to the mean of six determinations

Table 2: Evaluation data of robustness study

	Robust conditions	% Assay	System suitability parameters	
			Theoretical plates	Asymmetry
Telmisartan	Flow 0.27 ml/min.	98.30	4501	1.21
	Flow 0.23 ml/min.	99.62	4684	1.05
	Buffer-ACN (34: 66, v/v)	98.50	4568	1.38
	Buffer-ACN (30: 70, v/v)	99.73	4432	1.54
	Column change	99.48	4598	1.63
Cilnidipine	Flow 0.27 ml/min.	99.26	7318	0.95
	Flow 0.23 ml/min.	98.84	7066	1.12
	Buffer-ACN (34: 66, v/v)	100.83	7158	1.09
	Buffer-ACN (30: 70, v/v)	98.92	7469	0.99
	Column change	99.93	7425	0.92

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	99.61	99.66	99.63	99.59
12 h	99.80	99.76	99.83	99.54
24 h	99.73	99.79	99.61	98.90
36 h	99.54	99.98	99.55	99.26
48 h	99.73	98.96	99.70	98.96

Table 4: Evaluation data of system suitability study for Telmisartan

System suitability data	RSD (%)	Theoretical plates	Asymmetry
In-House limit	NMTb2.0	NLTc2000	NMTb2.0
Specificity	1.02	3628	1.24
Linearity	0.53	3290	1.46
Precision	0.20	3799	1.34
Intermediate	0.36	3730	1.38
Precision	0.83	3528	1.29
Accuracy	0.16	3026	1.20
Solution stability	0.71	3413	1.45
Robustness			

Table 5: Evaluation data of system suitability study for Cilnidipine

System suitability data	RSD (%)	Theoretical plates	Asymmetry
In-House limit	NMTb2.0	NLTc2000	NMTb2.0
Specificity			
Linearity	1.02	3628	1.24
Precision	0.53	3290	1.46
Intermediate	0.20	3799	1.34
Precision	0.36	3730	1.38
Accuracy	0.83	3528	1.29
Solution	0.16	3026	1.20
stability	0.71	3413	1.45
Robustness			

99.89% and 0.43% respectively for assay on different days (inter day). For assay of Cilnidipine (n=6), RSD of system precision was 1.45% on the same day (intra-day) and 1.02% on different days (inter-day). The mean values of % assay and % RSD for method precision (repeatability) were 99.35% and 1.41% respectively for assay on same day (intra-day) while, 99.09% and 0.98% respectively for assay on different days (inter day). Intermediate precision was established by determining the overall (intraday and inter day) method precision. For intermediate precision (n=12), overall % assay and % RSD value was 99.85% and 0.53% respectively for Telmisartan while, 99.72% and 1.22% for Cilnidipine. The precise result for content uniformity was indicative of uniform distribution of the drug in the tablets without significant variation; this is 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, 150µg/ml) for Telmisartan and (12.5, 25.0, 37.5µg/ml) for Cilnidipine were added to a placebo preparation and the amount of Telmisartan and Cilnidipine recovered, in the presences of placebo interface, was calculated. The mean recovery of Telmisartan was 99.20%, 100.03% and 99.26% respectively and the mean recovery of Cilnidipine was 98.11%, 99.46% and 99.12% respectively (Table I). 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 II). The analytical method therefore remains unaffected by slight but deliberate

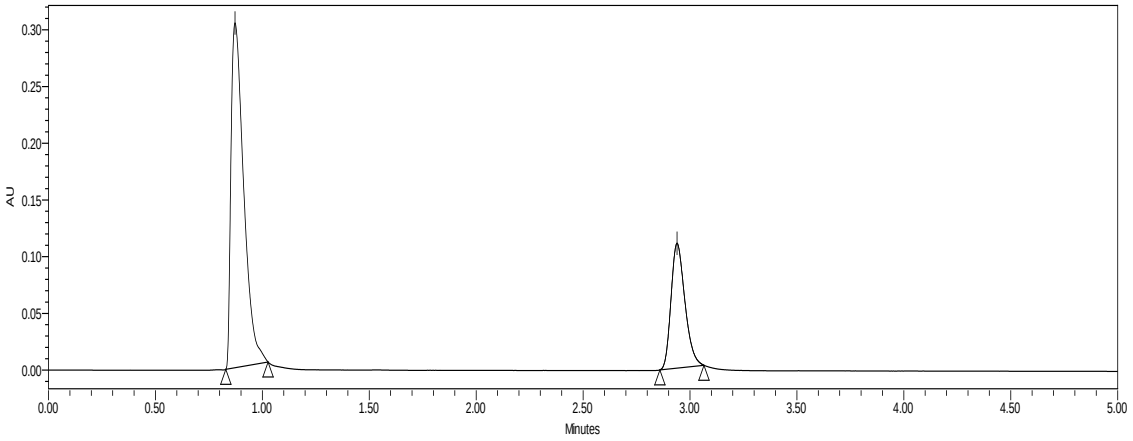

Figure 3: Chromatogram of standard preparation

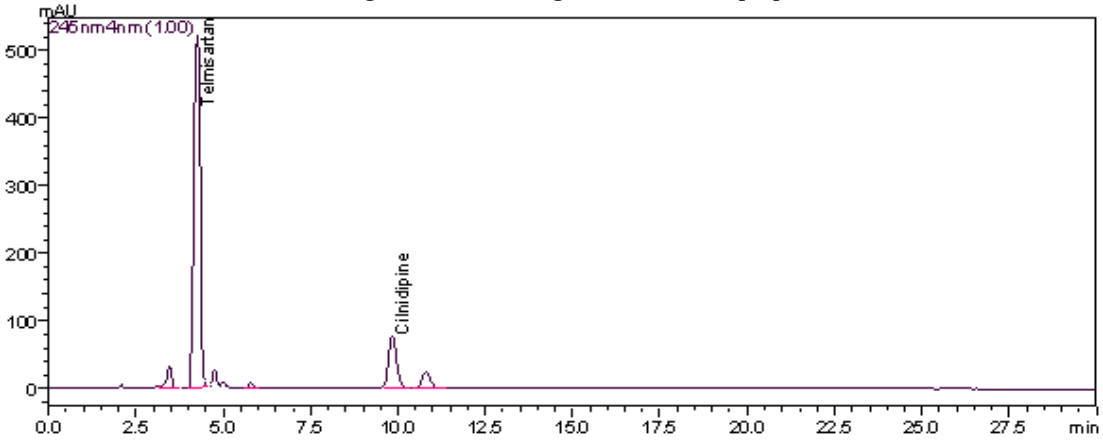

Figure 4: Chromatogram of alkali forced degradation study

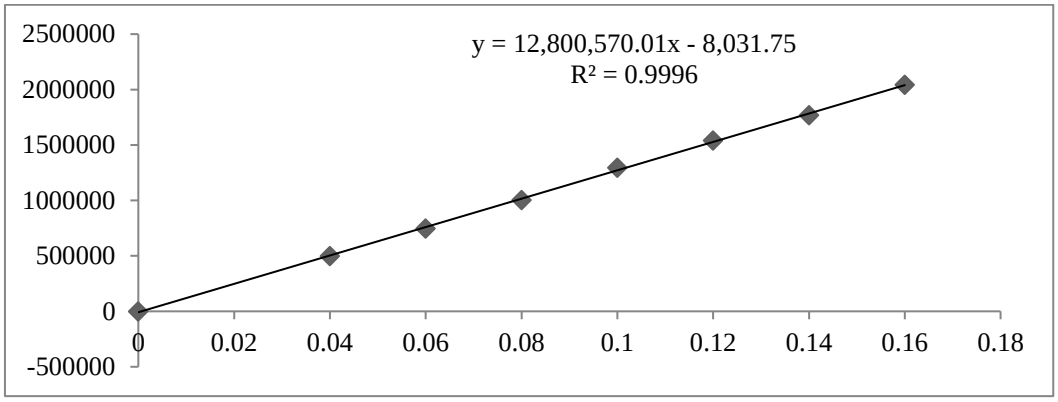

Figure 5: Linearity curve for Telmisartan

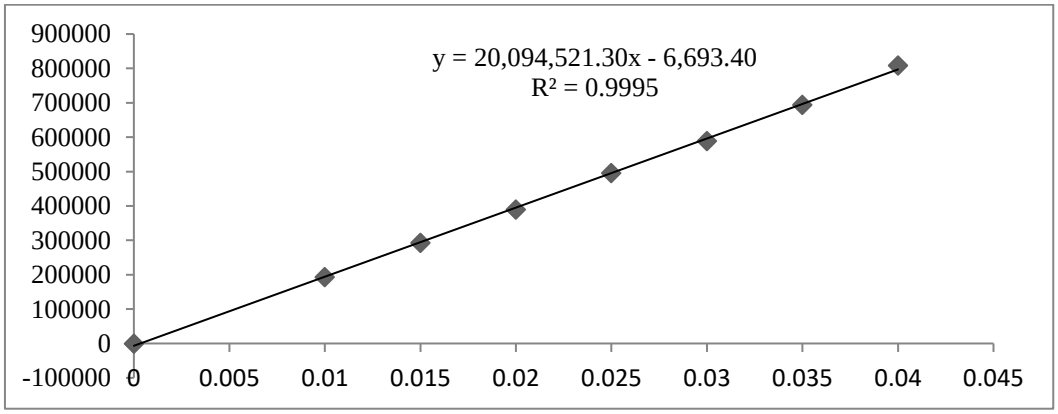

Figure 6: Linearity curve for Cilnidipine

changes in the analytical conditions. During 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 48hr. Assay values obtained after 48hr were statistically identical with the initial value without measurable loss (Table III). 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 a standard solution. The values obtained were satisfactory and in accordance with in-house limits (Table IV & V).

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 and robust and stability indicating. Hence, the method is recommended for routine quality control analysis and also stability sample analysis.

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