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Development and Validation of Fast and Robust Stability Indicating RP-HPLC Method for Simultaneous Estimation of Azilsartan Medoxomil and Cilnidipine in Pharmaceutical Dosage Form

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ABSTRACT

Objectives: A selective, precise and accurate RP-HPLC stability indicating assay method has been developed for the simultaneous estimation of Azilsartan medoxomil and Cilnidipine in tablet dosage form. **Materials and Methods:** The efficient chromatographic separation of drug was achieved by using C_{18} (150mm×4.6mm, Agilent 5µm) Column at ambient temperature. Mobile phase contains triethylamine buffer (pH 3.5 adjusted with ortho-phosphoric acid) and acetonitrile (40:60 V/V). Flow rate of mobile phase 1.0 ml/min using isocratic mode .Wavelength selected at 249 nm by using photo diode array detector. **Results:** The retention time of Azilsartan medoxomil peak 1, Azilsartan medoxomil peak 2 and Cilnidipine were noticed to be 2.16 min, 3.90 min and 9.52 min respectively. The linearity range for Azilsartan medoxomil and Cilnidipine were found to be 50 -150 µg/ml and 12.5-37.5 µg/ml and percent recoveries were noticed to be 99.27±0.58 and 98.65±0.49 respectively. Various stress testing conditions such applied to the drug ingredients and drug formulation. The degradants and drugs efficiently separated by using enhanced chromatographic conditions. The developed method was validated as per recommendation parameters of International council on harmonization guideline Q2(R1). **Conclusion:** The validation parameters stated that the drug substances were efficiently separated from its degradants and developed method can be routinely applied for the simultaneous estimation of Azilsartan medoxomil and Cilnidipine in tablet formulation in a laboratory.

Keywords: Azilsartan medoxomil, Cilnidipine, RP-HPLC, Stability Indicating, ICH Q2(R1).

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INTRODUCTION

Azilsartan medoxomil (5-methyl -2-oxo-1,3-dioxol-4-yl)-2-ethoxy-3-[[4-[2-(5-oxo-4H-1,2,4-oxodiazol-3-yl] phenyl] methyl] benzimidazole-4-carboxylate falls under a category of anti-hypertensive drugs called ARB blocker. It selectively binds to Angiotensin -1 receptors as antagonist, blocking vasoconstrictor and aldosterone – secreting effects of angiotensin –II.[1] It is not reported officially in the United States Pharmacopoeia, British Pharmacopoeia and Indian Pharmacopoeia. Cilnidipine 3-0-(2- methoxyethyl) 5-0[(E)-3-phenylprop-2-enyl]-2-enyl] 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine -3,5-dicarboxylate,[2] which is a calcium channel blocker acts on the L-type channel of blood vessel by blocking the incoming calcium and suppressing the contraction of blood vessels, thereby reducing blood pressure.[3] It is reported officially in Indian Pharmacopoeia (IP)-2018.[4] Literature study revealed that the analytical techniques like HPTLC,[5-6] HPLC,[7-8] UV-spectrophotometry,[9,10] LC/MS-MS[11-12] methods have been presented for determination of Azilsartan medoxomil and Cilnidipine as a single, while for the combination of Azilsartan medoxomil and Cilnidipine method is available on UV- spectroscopy[13] and HPLC,[14] there is no article related to Stability Indicating HPLC Assay method to quantify Azilsartan medoxomil and Cilnidipine in bulk has ever been mentioned within literature referred. The primary goal of this project was to produce a specific, accurate, and reproducible stability indicating HPLC methods for determination of Azilsartan medoxomil and Cilnidipine as stated in the ICH guidelines.[15] Figure 1 describe the chemical structure of Azilsartan medoxomil and Cilnidipine.

MATERIALS AND METHODS

Reagents and Chemicals

Various Reagents and chemicals used in this work listed below in Table 1.

Instrumentation

Instruments used in this work are listed below in Table 2.

Preparation of mobile phase

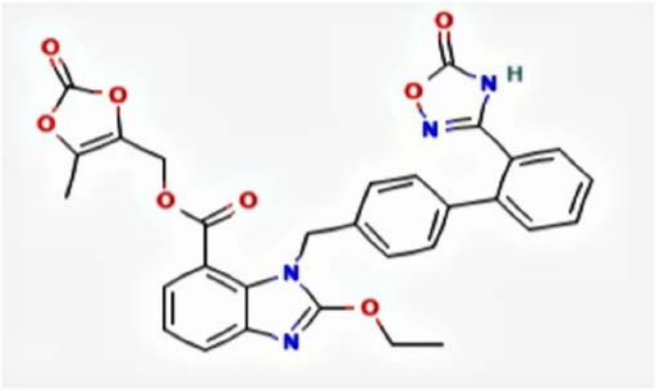
Mobile phase consisted of 0.035M triethylamine buffer (pH 3.5) and acetonitrile in ratio of 40:60. The buffer solution was filtered through 0.45 µm membrane filter and degassed before use.

Preparation of diluent

The diluent is made up of 0.035M triethylamine buffer (pH 3.5) and acetonitrile in 50:50 v/v ratio.

Preparation of standard and stock solution

The stock solution was made by weighing 40 mg of Azilsartan medoxomil and 10 mg of Cilnidipine accurately into volumetric flask of 100 ml. 30 ml of methanol was added and sonicated to dissolve. Volume made upto mark using methanol, (400 µg/ml and 100 µg/ml) concentration of both drugs respectively. 2.5 ml of standard stock solution was further diluted upto 10 ml using diluent to get (100µg/ml and 25µg/ml) concentration of both drugs respectively.



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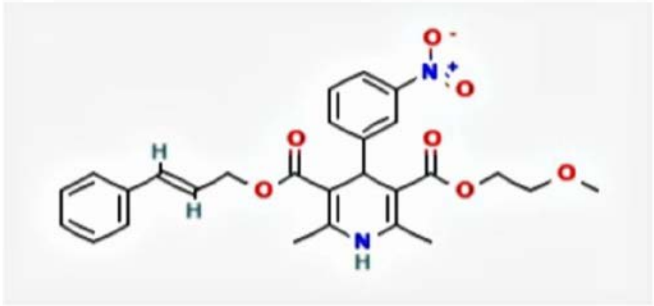

Figure 1: (A) Chemical structure of Azilsartan medoxomil (B) Cilnidipine.

Table 1: Chemicals and Reagents

Sl. No	Reagents	Grade	Manufacturer
1.	Methanol	HPLC Grade	Rankem lab.
2.	Acetonitrile	HPLC Grade	Rankem lab.
3.	Sodium Hydroxide	AR Grade	Central Drug House (p)Ltd.
4.	Hydrochloric Acid	AR Grade	Rankem lab
5.	Hydrogen Peroxide	AR Grade	Central Drug House (p) Ltd.
6.	Triethylamine	AR Grade	Rankem lab.
7.	Ortho-Phosphoric Acid	AR Grade	Central Drug House (p) Ltd.
8.	Water	HPLC Grade	Mili-Q
9.	Tablet Dosage Form (MYOTAN CN 10) (Azilsartan medoxomil 40 mg + Cilnidipine 10 mg)	--	Synokem pharmaceuticals Ltd. Haridwar

Chromatographic Conditions

The optimized various chromatographic conditions for this work listed below in Table 3.

Preparation of sample for commercial formulation

The commercial formulation (MYOTAN® CN) tablets contained 40 mg of Azilsartan medoxomil and 10 mg of Cilnidipine. Weighed and powdered of 20 tablets. Accurately weighed a tablet powder was equivalent to 40mg of Azilsartan medoxomil and 10mg of Cilnidipine. Then transfer it into 100 ml volumetric flask, solubilized in 30 ml of methanol solvent, sonicated with intermittent shaking for 15 min. Further dilute it upto mark with methanol to achieved (400 µg/ml and 100 µg/ml Concentration) Further centrifuge it at 3000 rpm fort 10 min. Take 2.5 ml from the supernant solution and transfer it into 10 ml of volumetric flask and dilute upto mark using diluent to get (100 µg/ml and 25 µg/ml concentration) of each drug respectively.

Table 2: Various Instruments using in this work.

Sl. no.	Instruments	Model no.	Manufacturer
1	HPLC	1260 Infinity II	Agilent
2	HPLC Column	Eclipse Plus C_{18} (150mm x 4.6mm, 5µm)	Agilent
3	Detector	Photo Diode Array	-
4	FT-IR	IR Spirit	Shimadzu
5	UV-Visible Spectrophotometer	UV- 1900	Shimadzu
6	PH meter	EQ-610	Lab Line
7	Ultra Sonicator	LMUC 6	-
8	Water purification system	-	Mili- Q
9	Analytical Weighing Balance	ME204/A04	Shimadzu
10	Centrifuge	CPR-24 Plus	Remi

Table 3: Optimized Chromatographic conditions.

Mode of elution	Isocratic
Column	Eclipse plus C_{18} (150mm × 4.6mm, Agilent 5µm)
Mobile phase	0.035M TEA buffer (pH- 3.5): ACN (40:60V/V)
Flow Rate	1ml/min
Detection wavelength	249nm
Injection volume	10µL

MATERIALS AND METHODS

Range and Linearity

Fixed standard aliquots (1.25-3.75 ml) of Azilsartan medoxomil and Cilnidipine transferred in different five volumetric flask and dilute it upto 10 ml using diluent to have final range of concentration was 50-150 µg/ml of Azilsartan medoxomil and 12.5-37.5 µg/ml of Cilnidipine. Accordingly, to that 10 µL volume of sample was injected into the RP-HPLC with the help of auto sampler and chromatographic condition. The peak area vs concentration was used to plot the calibration curve. The slope, intercept and regression line equation were found from the calibration graph.

Accuracy

Turness (closeness to the true value) of the quantification method were determined from the % recovery of Azilsartan medoxomil and Cilnidipine at 3 different levels of 50 %, 100%, 150% of target concentration by injecting in triplicates. The fixed volume of sample solution was injected in chromatograph.

Precision

Method precision (closeness of agreements measured by changing the different instances) was examined through interday and intraday

analysis samples. For Intra-day analysis three replicates of samples (n=3) each of limit level of Azilsartan medoxomil (100 µg/ml) and of Cilnidipine (25 µg/ml) were analyzed on the present day. Whereas inter day analysis, sample were analyzed on three separate days by using the same chromatographic conditions and same sample concentration that are freshly prepared. % RSD were calculated to evaluate the method precision.

Sensitivity (Quantitation limit)

The detection and quantitative limits (LOD and LOQ) were calculated as per equation of the ICH guidelines: LOD = 3.3(SD)/S and LOQ = 10(SD)/S, where SD = standard deviation of peak and S= average slope of calibration curve.

Robustness

It's an ability of the entire methodology to remain unaltered by a small and intentional change in different parameters was checked. change in temperature, flow rate, wavelength were examined keeping other chromatographic condition same. In triplicate, samples injections was injected into chromatograph and chromatogram developed using optimized chromatographic conditions.

Force Degradation Studies

Force degradation studies of API and tablet formulation were performed under acid and alkali hydrolysis, thermal, photolytic and oxidative degradation.

In the Table 4. various stress testing conditions were given.

RESULTS

Development and Optimization of Method

The separation and estimation of drugs in presence of its degradants was done using isocratic mode on Eclipse plus C_{18} (150mm×4.6mm, 5µm) reverse phase column with 1.0 ml/min flow rate, mobile phase having composition of 0.035M triethylamine (pH 3.5 adjusted with ortho-phosphoric acid) and acetonitrile (ACN) in ratio of 40:60 v/v was optimized and resulted in well-resolved and good sharp peaks in presence of degradation products and impurities. The 10µL sample solution was injected using autosampler. Wavelength of 249nm was optimized as detection wavelengths for Azilsartan medoxomil and Cilnidipine (Figure 2). The retention time Azilsartan medoxomil and Cilnidipine under optimized conditions was 3.90 min and 9.62 min

Table 4: Various Stress testing Conditions

Forced degradation studies name	Conditions	Final Concentration of Sample(µg/ml)	
		Azilsartan medoxomil	Cilnidipine
Acid Hydrolysis	5N 1ml Hcl for kept at room temp. for 1 hr.	100	25
Base Hydrolysis	5N 1ml NaOH kept at room temp. for 1 hr.	100	25
Oxidative degradation	1 ml 3% H_2O_2 kept at room temp. for 1 hr.	100	25
Thermal Degradation	Kept at 80°C for 45min	100	25
Photolytic Degradation	Under UV light for 24 Hrs	100	25
Uv Control Degradation	Under UV light wrapped with AL foil for 24 Hrs.	100	25

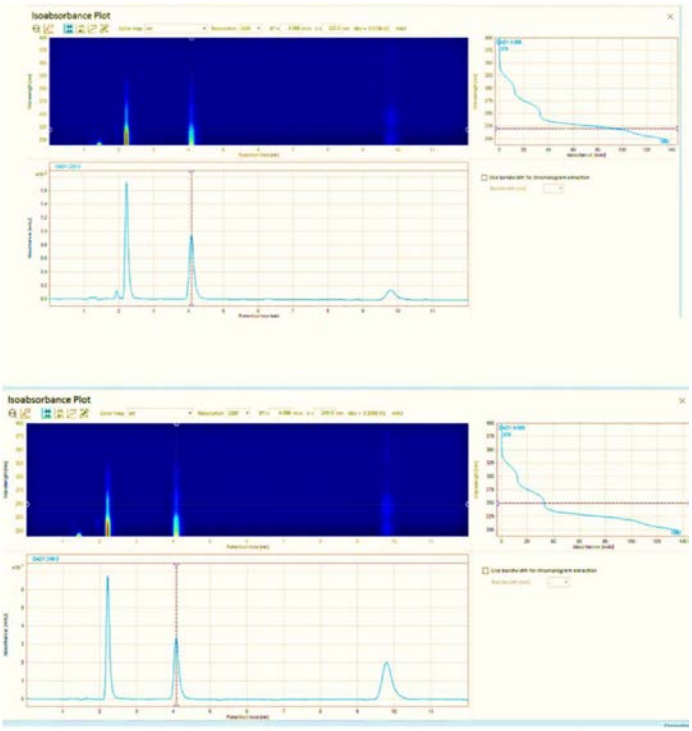

Figure 2: Isoabsorptive wavelength selected 249 nm for Azilsartan medoxomil and Cilnidipine.

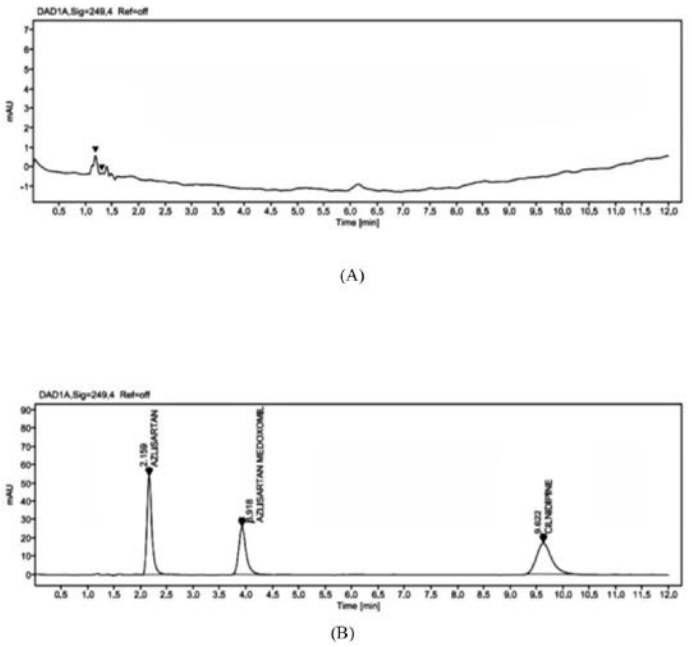

Figure 3: Typical HPLC chromatogram of (A) Blank (B) standard mixture of drugs (Retention time of Azilsartan medoxomil=3.90 min and Cilnidipine= 9.59 min).

Table 5: System suitability parameters of Azilsartan medoxomil and Cilnidipine.

Parameters	Results of Azilsartan medoxomil	Result of Cilnidipine
%RSD of peak area	1.06	0.69
Retention time	2.16 min, 3.90 min	9.59 min
Theoretical plates (N)	4003	5581
Tailing factor (T)	1.28	1.30
Resolution (R)	8.56	14.94

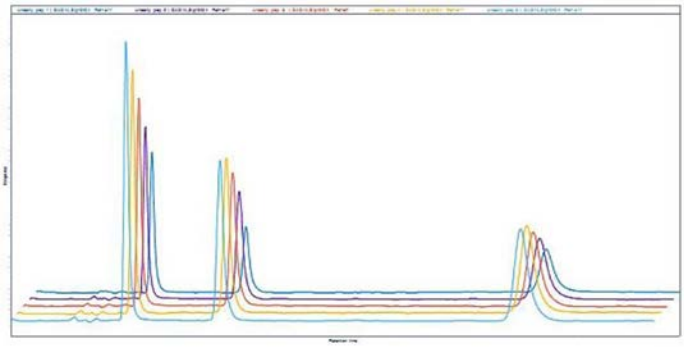

Figure 4: Linearity overlay.

respectively (Figure 3). The various system suitability parameters were observed and found within specified limits according to ICH guideline. The parameters of system suitability were observed within specified limits (Table 5).

Range and Linearity

Linearity of method was checked by analytical five different concentration levels of the standard drug solution of Azilsartan medoxomil and Cilnidipine separately. The linearity for Azilsartan medoxomil was found to be 50 -150µg/ml and Cilnidipine was found to be 12.5-37.5 µg/ml. The correlation co-efficient were found to be 0.999.4 and 0.9995 for Azilsartan medoxomil and Cilnidipine respectively and their equation of regression was calculated from calibration curve. Figure 4 shows linearity overlay.

VALIDATION

Precision and Accuracy

%RSD for repeatability of method, interday and intraday precision were observed below 2 % state that developed method is precise. The recovery were performed in order to estimate accuracy of analytical method, known concentration of standard drug was added into pre-analyzed sample at three separate levels, 50,100,150 %. %recovery of drug was calculated from the regression equation (Table 6).

Sensitivity and Specificity

The standard deviation and slope of the calibration plots were used to evaluate the detection and quantitation limits. LOD of Azilsartan medoxomil and Cilnidipine were 0.61µg/ml and 0.91µg/ml respectively. LOQ of Azilsartan medoxomil and Cilnidipine were 1.86 µg/ml and 2.78 µg/ml respectively. The developed method was able to distinguish other excipients that are found in the tablet from the two drugs and was therefore can be stated specific. The peak purities and chromatograms of the Forced degradation sample indicate the specificity of the method.

Table 6: Accuracy data of Azilsartan medoxomil and Cilnidipine.

Azilsartan medoxomil				
Parameters	Amount added	Amount Recovered	%Recovery mean±SD (n=3)	Mean% Recovery
50%	150 ppm	148.5	99±0.45	
100%	200 ppm	198.7	99.35±0.73	99.27±0.58
150%	250 ppm	248.7	99.48±0.58	
		Cilnidipine		
50%	37.5 ppm	36.9	98.4±0.29	
100%	50 ppm	49.1	98.2±0.63	98.65±0.49
150%	62.5 ppm	62.1	99.36±0.55	

Table 7: Summary of method validation parameters.

Parameters	Azilsartan Medoxomil	Cilnidipine
Linearity (µg/ml)	50-150	12.5-38.5
Slope (m)	5.085	15.001
Intercept (c)	+100.93	-18.554
Correlation coefficient (r^2)	0.9995	0.9994
Regression equation	Y=5.0859x + 100.93	Y=15.001x – 18.554
LOD (µg/ml)	0.61	0.91
LOQ (µg/ml)	1.86	2.78
Precision		
Repeatability (%RSD, *n*=6)	1.51-1.89	1.42-1.73
Intraday (*n*=3)	1.25-1.53	1.32-1.67
Interday (*n*=3)	1.35-1.83	1.2-1.72
Robustness (%RSD)		
Flow rate change	0.75-0.98	0.43-0.62
Column temperature change	0.55-0.64	0.32-0.59
Wavelength change	0.47-0.78	0.65-1.03

The robustness of method were checked by injecting sample with small changes in the chromatographic conditions like, change in temperature, wavelength, flow rate and mobile phase pH and the % relative standard deviation (% RSD) of each variable was calculated (Table 7).

Stress Degradation

The forced degradation studies indicate that the drugs were sensitive to acid, alkali, oxidation and thermolytic degradation conditions. Chromatograms of several forced degradation conditions of sample shown that the drug substances were well separated from impurities and degradants (Figure 5). The % degradation of drugs were evaluate by computing areas of drugs in each condition with respective peak areas of drugs under normal condition (Table 8).

Assay of Marketed Formulation

The sample was prepared from commercial formulation (tablets) as per procedure (Azilsartan medoxomil 40 µg/ml and Cilnidipine 10 µg/ml). Marketed formulation assay was performed under the optimized chromatographic conditions using triplicates. The average of % content of Azilsartan medoxomil and Cilnidipine from curves of calibration were

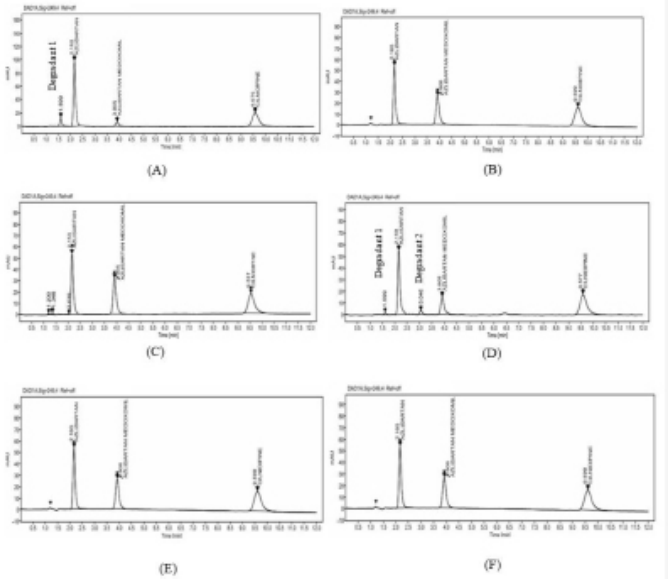

Figure 5: Chromatogram of forced degradation (A) acid degradation (B) base degradation (C) oxidative degradation (D) thermal degradation (E) photolytic degradation in UV expose (F) and UV control.

Table 8: Summary of forced degradation study.

Sr. No	Type of Degradation	Stress Conditions	% Degradation Observed	
			Azilsartan medoxomil	Cilnidipine
1	Acid Hydrolysis	5N HCL /80°C/1hr	24%	16%
2	Alkali Hydrolysis	5N NaOH /80 °C/1hr	19%	11%
3	Oxidative degradation	3% H_2O_2 /Room temp. /1hr	11%	5%
4	Thermal Degradation	1hr /80°C	17%	8%
5	UV Exposure	Exposed to the UV light (254nm) /24hrs	1.2%	1.5%
6	UV Control	Control from the UV light (254nm) /24hrs	1%	1.2%

found to be 99.07 and 99.05 respectively. None of the tablet excipient interfere with the analyte peak. The % relative standard deviation for all method parameters were observed to be within acceptable limits, which shows the method validity and % drug content by this method are in acceptable limits.

Solution stability

The stability of samples was evaluated at periodic intervals of 4 hrs., 6 hrs., 12 hrs., 24 hrs. and 48 hrs. at ambient temperature. The sample's peak area was calculated at particular intervals by using optimized chromatographic conditions. From the results say sample solution were stable even after48 hrs. at an ambient temperature.

DISCUSSION

In this developed method, the drug substances having different physiochemical properties. Appropriate analytical wavelength was identified using detector called photodiode array for the simultaneous estimation of Azilsartan medoxomil and Cilnidipine. Various mobile phase composition were tried for successful separation of drugs in the presence of degradants according to available literature. The various chromatographic factors like wavelength detection, stationary phase, pH of mobile phase and composition and flow rate of mobile phase were evaluated so that chromatographic conditions get optimized. In this work, various mobile phase composition used like Methanol, water, Acetonitrile in different ratios but it shows poor resolution and peak broadening Thus, buffer solution was applied so that chromatographic conditions got optimized. Mobile phase with composition of 0.035M triethylamine (pH-3.5 adjusted with O- phosphoric acid) and Acetonitrile (40:60 v/v) shown efficient and better separation of drug substances and their degradants formed during forced degradation study.

System suitability of method was examined by checking the various system suitability parameters The project work was carried out on Eclipse C_{18} (150mm × 4.6 mm, Agilent 5µm) column at room temperature which showed better reproducibility The results of system suitability parameters was found to be within specified limits as per ICH guideline.

The estimation detection and quantification limit values confirmed that method was sufficiently sensitive for the detection of drug in the presence of their degradants. Along with % recoveries of the drug were observed to be within specified limits. Method's specificity was evaluated by injecting blank, standard, sample and performing forced degradation. The statistical data obtained during robustness study shows that the method which is developed is robust.

In the stress degradation study, it was observed that both drugs were susceptible to hydrolysis, oxidation and thermolysis. Azilsartan medoxomil shows one degradant in acidic condition showing that it is more sensitive to the acidic condition (5N HCL). Cilnidipine was less sensitive to acid and alkali conditions as compared to Azilsartan medoxomil. Azilsartan medoxomil and Cilnidipine were equally susceptible in oxidative degradation condition. Under thermal degradation two degradants were observed in Azilsartan medoxomil. From the above it was concluded that the degradants peak does not interfere with standard drug peak.

CONCLUSION

A specific, rapid, accurate and precise stability – indicating HPLC method was developed for the quantitation of Azilsartan medoxomil and Cilnidipine in the combined tablet. The method validation suggests that successful separation two drugs with its degradants was possible using these methods. The developed RP-HPLC method stability indicating assay method could be frequently used in the quality control department for the quantitative estimation of drugs.

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ABBREVIATIONS

ICH: International Council on Harmonization; **RP-HPLC:** Reversed Phase High Performance Liquid Chromatography; **DAD:** Diode Array Detector; **LOD:** Limit of detection; **LOQ:** Limit of Quantitation; **SD:** Standard Deviation; **RSD:** Relative Standard Deviation; **RS:** Reference Standard; **HPTLC:** High Performance Thin Layer Chromatography; **LC-MS:** Liquid Chromatography Mass Spectrometry; **UV:** Ultra Violet; **AR:** Analytical Reagent; **RS:** Reference standard **HCL:** Hydrochloric acid; **NaOH:** Sodium hydroxide; **Hrs.:** Hour.

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