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STABILITY INDICATING VALIDATED RELATED SUBSTANCE UFLC METHOD & ALKALI DEGRADATION IMPURITIES CHARACTERIZED BY LCMS FOR IRBESARTAN IN BULK AND PHARMACEUTICAL FORMULATION PRODUCT

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ABSTRACT

This work emphasis the base decomposition of the Irbesartan and identification of new impurity determined by Ultra speed separation (UFLC) technique. The stress studies were carried out as per ICH guidelines Q1A R2, Q1B for the Irbesartan i.e., Hydrolytic, Oxidative, Photolytic and Thermal stress. A simple, highly economic, rapid, and sensitive reversed phase Ultra fast liquid chromatographic method developed for Irbesartan with potential impurities and degradation impurities. The chromatographic separation for five impurities and three new degradation impurities were achieved by using Rapid resolution Symmetry C18 2.1 x 50mm, 1.7µm. This method is applicable of Irbesartan both in the bulk and formulations. The newly developed method was validated according to the ICH guidelines with respect to specificity, linearity, accuracy, precision and robustness.

Keywords: UFLC, Irbesartan, Method validation and Forced degradation.

INTRODUCTION

Hypertension is now a common threatening disease in the present days. Discovery of many drugs came for treatment of Hypertension .The molecule class of sartan family which plays a vital role in the treatment of Hypertension. Irbesartan (II) is chemically 2-butyl-3-[[2-(tetrazol-5-yl) biphenyl-4-yl]-methyl]-1, 3-diazaspiro[4.4]non-1-en-4-one, acts as angiotensin-II receptor subtype I(AT1) antagonist, used mainly for the treatment of Hypertension. It has an empirical formula of $C_{25}H_{26}N_6O$ and molecular weight of 428.53. Irbesartan is a white to off white crystalline powder and is slightly soluble in alcohol and methelyene dichloride and practically insoluble in water. A variety of UV procedures were reported for the determination of Irbesartan as single compounds or in mixtures.Amit Asati[1] reported a Quantitative analysis and validation for Irbesartan in bulk drug by Ultra violate Spectroscopy. Srikanth Nissankararao[2] reported Estimation of Irbesartan in bulk and dosage forms by new simple UV Spectroscopy. Derivative spectroscopic method for estimation of Irbesartan in bulk Drug and Dosage form has been reported by PP.Dhanawade and RN.Kane[3]. Ramzia.I.El-Bagary[4] Reported Spectroflurometric, Spectrophotometric and LC Determination of Irbesartan. A variety of UV procedures were reported for the determination of Irbesartan as in mixtures[5-7].

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V.Bhaskara Raju[8] reported a validated RP-HPLC method for the estimation of Irbesartan in bulk and tablet dosage form. Praveen Kumar. M[9] reported a Development and validation of a stability-Indicating RP-HPLC method for assay of Irbesartan in pure and pharmaceutical dosage form.R.Ramesh raju[10] reported a Development and validation of HPLC method for the estimation of Irbesartan in pharmaceutical dosage form. A variety of HPLC procedures were reported for the determination of Irbesartan as in mixtures[11-14].P.Prabhu[15] reported a Development & validation of High performance liquid chromatography method for simultaneous determination of Irbesartan and its related impurities in pharmaceutical Tablets. Development and validation of stability indicating UPLC method for the simultaneous determination of beta-blockers and diuretics drugs in pharmaceutical dosage form has been reported by Lakshmi Narasimham Y.S[16]. M.Ganesan[17] reported a Method development and validation of Irbesartan using LC-MS/MS.The drug was subjected to stress studies as per ICH-guidelines new impurities was identified in the alkali degradation with the help newly developed UFLC Method and also confirmed by the pharmacopeia method. The newly developed UFLC method was validated as per ICH-guidelines. This method can be used for evaluating the drug in the presence of its-degradation products. But the newly developed ultrafast liquid chromatography (UFLC) method was able to resolve the process impurity and the degradation impurity have evolved as the advantageous technique for the analysis of APIs and

impurities within a short interval of time. The Irbesartan structure is given in the Fig.1.0.

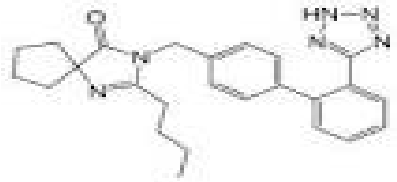

Fig. 1: Chemical structure of Irbesartan

2. EXPERIMENTAL

2.1 Chemicals and Reagents

Standard and samples of Irbesartan and its five impurities namely Imp-A ,Imp-B, Imp-C, Imp-D and Imp-E were obtained from Madras pharmaceuticals (Karapakkam ,India).The formulated Irovel(Irbesartan USP) 150mg and 300mg samples was purchased from commercial shops. All reagents used were of AR grade unless stated otherwise. HPLC grade Acetonitrile, Methanol, Water was purchased from J.T.Baker (Phillipsburg, NJ, USA). HPLC grades Ammonium Acetate, Orthophosphoric acid, Triethylamine were purchased from Merck (Darmstadt, Germany). The Sodium Hydroxide, Hydrochloric acid, and Hydrogen peroxide was purchased from Ranbaxy Labarotories.Dueterated methanol, water, Dimethyl sulfoxide was obtained from Sigma Aldrich

2.2 Instruments and Apparatus

The UFLC system was equipped with binary gradient pumps with auto sampler and auto injector (Model Prominence UFLC XR , PUMP LC-20AD , AUTO INJ SIL-20AC, OVEN CTO-20AC , PDA detector SPD-M20A, Dual UV detector SPD-20A , Make SHIMADZU JAPAN controlled with Empower software (Make: Waters, USA). Mettler Tolexdo Microbalance MX-5 was used for weighing throughout the complete validation experiment. To aid dissolution of the standards and sample in solution Soniclean ultra sonicator was used. The column used was Rapid resolution Symmetry C18 2.1 x 50mm, 1.7µm

2.3 Methodology

After conducing of many Trails the optimized conditions were set for this method. optimized conditions are follows; Stationary phase Symmetry C18 2.1 x 50mm, 1.7µm,Mobile phase consist of 0.02M ammonium acetate in water in Pump A and 60:40 Acetonitrile and methanol premixed and sonicated in the Pump B .Flow rate is 1.0ml/min ,column temperature is 30°C,cooler temperature is 15°C ,injection volume is 5µl and the detection wavelength is 220nm.The gradient condition is T min ,A:B; T0.01,75/25; T8.50,10/90; T11.50,10/90; T11.51, 75/25; T12.00, 75/25.Diluent is (1:1) water: Acetonitrile UFLC Rinsing solution is the same as the diluent.

2.3.1 Irbesartan stock solution preparation

Stock solution of the Irbesartan is prepared by dissolving accurately weighed 50mg of Irbesartan standard into 100mL volumetric flask and make up the volume with Mobile phase.Fig.No:2 showed the standard chromatogram.

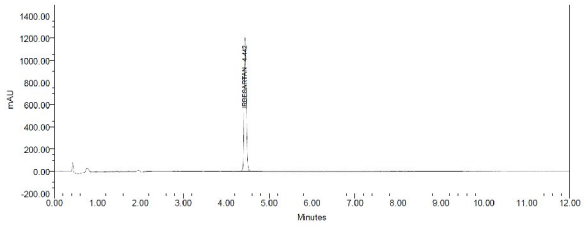

Fig. 2: Standard Chromatogram

2.3.2 Impurity stock solution preparation

Weighed 2.5mg of each impurity (IMP-A, IMP-B, IMP-C IMP-D and IMP-E) and transfer into 100mL volumetric flask make up the volume with mobile phase.

2.3.3 Sample Preparation

2.3.3.1 API Preparation

To estimate the content of drug present in the API. The API sample Irbesartan is prepared by dissolving accurately weighed 50mg of Irbesartan standard into 100mL volumetric flask and make up the volume with Mobile phase.

2.3.3.2 Formulation (Sample) Preparation

To estimate the amount of drug content present in tablets. 20 tablets of the pharmaceutical dosage form are weighed individually and their mean weight was determined. Crush and ground finely the above weighed tablets using mortar and pestle. An equivalent of 50 mg of Irbesartan was weighed accurately and transferred into a 100 ml volumetric flask respectively and the contents of the flask diluted with Mobile phase. The sample solution was sonicated for 15 minutes. Fig.No:3 showed the Sample chromatogram.

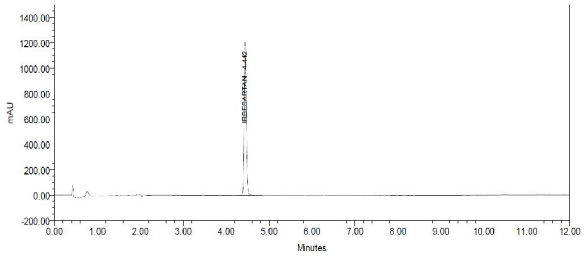

Fig. 3: Sample Chromatogram

2.3.3.3 Diluted standard preparation

Accurately weighed 50mg of Irbesartan standard into a 50mL volumetric flask. Made the volume with diluent and dissolved well. Further diluted 5mL of this solution into 50mL volumetric flask with diluent. Further diluted 1mL of this solution into 100mL volumetric flask with diluent.

3.0 Method Validation

3.1 System suitability

Accurately weighed 50mg of Irbesartan standard into a 100mL volumetric flask. Added 50mL of diluent and dissolved well. Added 4.0mL of each impurity stock

solution mixed well and dilute to volume with diluent and mixed well. Injected Diluent, System suitability (Fig.No:4) and RS Diluted standard into the system and results were coated in Table -1.

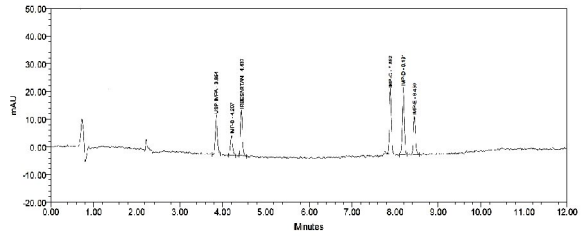

Fig. 4: System suitability Chromatogram

Table 1: System suitability results

Resolution Between Irbesartan and Imp-B	2.5
The number of theoretical plates for the Irbesartan peak	45344
The tailing Factor for the Irbesartan	1.25

3.2 Specificity

Specificity could be established by demonstrating that the procedure was unaffected by the presence of interference at the retention time of Irbesartan and its impurities with respect to mobile phase, diluent and Degradents. The Results were presented in Table-2. Fig.No:5 showed the Specificity chromatogram.

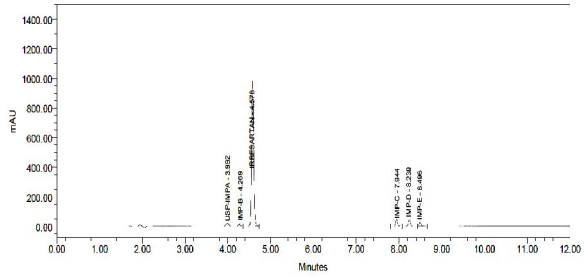

Fig. 5: Specificity chromatogram

Table 2: Specificity results

Diluent did not show any Interference.
Mobile phase did not showed any Interference.
Impurities and Degradents did not showed any Interference.

3.3 Precision

3.3.1 Method precision

Accurately weighed 50mg of Irbesartan tablet powder into a 100mL volumetric flask. Added 50mL of diluent and dissolved well. Added 4.0mL of each impurity stock solution mixed well and dilute to volume with diluent and mixed well. Injected Diluent, System suitability and Method precision samples into the system and results were coated in Table -3.

Table 3: Method Precision Data

Sample Name	Imp-A	Imp-B	Imp-C	Imp-D	Imp-E
Sample solution 1	0.18	0.19	0.49	0.51	0.52
Sample solution 2	0.19	0.19	0.50	0.51	0.51
Sample solution 3	0.19	0.19	0.49	0.50	0.52
Sample solution 4	0.19	0.19	0.50	0.51	0.51
Sample solution 5	0.18	0.19	0.50	0.50	0.50
Sample solution 6	0.18	0.18	0.50	0.51	0.50
Mean	0.19	0.19	0.50	0.51	0.51
%RSD	2.63	2.11	1.00	0.98	1.76

3.3.2 Intermediate Precision

The Intermediate precision could be carried out by performing six replicate analyses of Irbesartan tablets by spiking the impurities at 100% level spiked sample by different analyst on different day, with different chromatographic system, and with different chromatographic column than that utilized for repeatability test under the same chromatographic conditions and results were coated in Table -4.

Table 4: Intermediate Precision Data

Sample Name	Imp-A	Imp-B	Imp-C	Imp-D	Imp-E
Sample solution 1	0.19	0.19	0.49	0.51	0.49
Sample solution 2	0.19	0.19	0.50	0.51	0.50
Sample solution 3	0.19	0.18	0.49	0.50	0.49
Sample solution 4	0.19	0.19	0.50	0.51	0.50
Sample solution 5	0.19	0.19	0.50	0.50	0.50
Sample solution 6	0.19	0.19	0.50	0.51	0.50
Mean	0.19	0.19	0.50	0.51	0.50
%RSD	0.00	2.11	1.00	0.98	1.00

3.4 Linearity

Linearity could be established by demonstrating that the area response obtained is directly proportional to the concentration of standard solution and impurities solution. Linearity could be carried out by analyzing different levels ranging from 50 % to 150 % Levels and finding the response at each concentration level for Impurities & Irbesartan. The results are presented in Table-5.

Table 5: Linearity Table

Compound Name	Correlation Coefficient	RF Values
Imp-A	0.9999	0.96
Imp-B	1.0000	1.07
Imp-C	0.9997	1.06
Imp-D	0.9996	0.96
Imp-E	0.9999	1.02
Irbesartan	1.0000	NA

3.5 Accuracy

The Accuracy could be established by preparing three samples at three different levels (50%, 100% and 150%).The results are presented in Table-6.

Table 6: Summary data for Mean recovery

Recovery Level	Mean Recovery for IMP-A	Mean Recovery for IMP-B	Mean Recovery for IMP-C	Mean Recovery for IMP-D	Mean Recovery for IMP-E
50%	100.0	100.0	100.0	102.7	99.9
100%	101.3	102.7	105.0	100.0	100.2
150%	102.0	96.3	101.7	96.4	101.3
Mean	101.1	99.7	102.2	99.7	100.5
% RSD	1.01	3.21	2.54	3.21	0.74

3.6 Robustness

Robustness of the method was evaluated by deliberately modified the experimental conditions and there by estimated any change in the resolution between the impurities.

3.6.1 Solution stability (Standard and Sample)

To evaluate the solution stability, samples (prepared by spiking all known impurities at specification level) & standard are kept on bench top. Solutions were analyzed at initial, on day-1 (24 hours) and day-2 (48 hours) as per test method. The results are given in Table-7(a) & 7(b).

Table 7(a): Standard Solution stability results

Time Interval	Similarity Factor
Initial	NA
24 Hours	0.99
48 Hours	0.96

Table 7(b): Sample Solution stability results

Time	Imp-A (%)	%Diff	Imp-B (%)	% Diff	Imp-C (%)	%Diff	Imp-D (%)	%Diff	Imp-E (%)	% Diff	Total (%)	%Diff
Initial	0.19	NA	0.21	NA	0.50	NA	0.50	NA	0.50	NA	1.90	NA
24 Hours	0.20	0.01	0.20	0.01	0.52	0.02	0.52	0.02	0.52	0.02	1.96	3.10
48 Hours	0.23	0.04	0.25	0.04	0.51	0.01	0.51	0.01	0.51	0.01	2.01	2.53

3.6.2 Filter Validation

A study to establish the stability of filter could be conducted by using two different types of filters 0.45 µm Nylon and 0.45 µm GHP filters. Prepared the standard solutions; sample solutions spiked with all known impurities as per the method. Filter a portion of standard and sample solutions through 0.45 µm GHP membrane filter, 0.45 µm Nylon filter and centrifuge some portion of standard and sample solutions and analyze as per test method. Calculate similarity factor for the filtered standards against unfiltered standard (Centrifuged). Results are captured in Table-8(a) & 8(b).

Table 8(a): Standard Similarity Factor

Sample Name	Similarity Factor
Centrifuged sample	NA
0.45 µ GHP Filtered sample	1.00
0.45 µ Nylon Filtered sample	0.98

Table 8(b): Sample Filter validation Results

Sample Name	Centrifuged	GHP	Diff.	Nylon	Diff.
Impurity-A	0.19	0.20	5.13	0.19	0.00
Impurity-B	0.21	0.21	0.00	0.21	0.00
Impurity-C	0.50	0.51	1.98	0.51	1.98
Impurity-D	0.50	0.50	0.00	0.51	1.98
Impurity-E	0.52	0.51	1.94	0.50	3.92
Total Impurities	1.92	1.93	0.52	1.92	0.00

3.7 Changes in chromatographic conditions

The flow rate of the mobile phase was 1.0 mL/min. The effect of flow rate change was studied at the flow rates of 0.8 and 1.2 mL/min respectively, instead of 1.0 mL/min. The effect of the column temperature change was studied at 25°C and 35°C instead of 30°C. The effect of the percent organic strength change was studied by varying mobile phase-B by −5 to +5% and the effect of wavelength of the detector change were studied at 252nm and 256 nm. Results are captured in Table-9

Table 9: Results for Changes in Chromatographic conditions

Parameter	% RSD	Theoretical plates	Tailing factor	Resolution
Flow rate 0.8mL/min	2.234	48544	1.20	2.2
Flow rate 1.2mL/min	3.654	43256	1.23	2.6
Temp 25°C	2.124	42564	1.28	2.5
Temp 35°C	3.456	48566	1.30	2.6
Organic strengths change -5%	1.241	47555	1.10	2.4
Organic strengths change +5%	2.846	48656	1.30	2.8
Wave length at 222nm	2.689	46654	1.26	2.6
Wave length at 218nm	2.324	46565	1.28	2.5

4.0 Forced degradation

4.1 Acid degradation

Weigh 20 tablets of Irbesartan and crush the tablets. Weigh accurately the crushed sample powder equivalent to 50 mg of Irbesartan into 100 mL volumetric flask, to this add about 50 mL of diluent and sonicate for 10 minutes with occasional shaking add about 10 mL of 5 N HCl and heat the sample at 60°C for about 1 hour in water bath and Cool to room temperature then neutralize with 10 mL of 5N sodium hydroxide, and make up to the volume with diluent. Filter the supernant solution through 0.45µm GHP or finer porosity membrane filter. Injected these solutions into system and results are captured in Table-10.

4.2 Alkali degradation

Weigh 20 tablets of Irbesartan and crush the tablets. Weigh accurately the crushed sample powder equivalent to 50 mg of Irbesartan into 100 mL volumetric flask, to this add about 50 mL of diluent and sonicate for 10 minutes with occasional shaking to this add about 10 mL of 5N sodium hydroxide and heat the sample at 60°C for about 1 hour in water bath and Cool to room temperature then neutralize with 10 mL of 5N Hydrochloric acid and make up to the volume with diluent. Filter the supernant solution through 0.45µm GHP or finer porosity membrane filter. Injected these solutions into system and results are captured in Table-10. Fig.No:6 showed the Alkali degradation chromatogram.

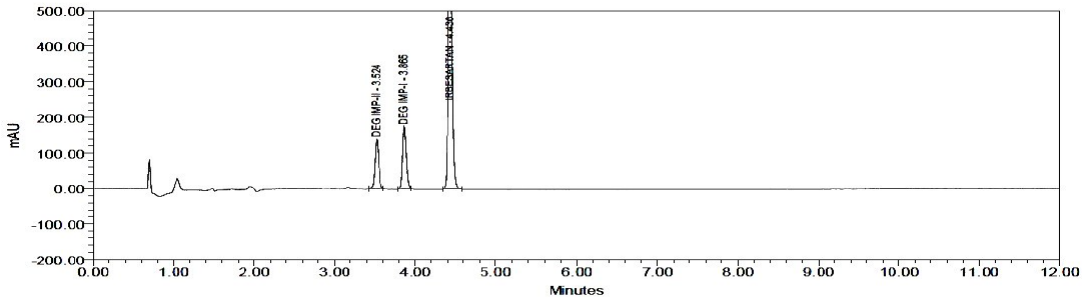

Fig. 6: Alkali degradation chromatogram

LC/MS characterization for Alkali Degradation impurity

The mass spectral analysis was carried out by direct infusion of 10ug/mL Alkali degradation solution into the ESI source at a flow rate of 10ul/min along with the mobile phase flow rate of 500ul/min .The obtained mass spectrum showed m/z 171 as a major ion which can be attributed to the MH^+ ion of the analyte. The mass spectral analysis was carried out by direct infusion of 10ug/mL Irbesartan standard solution into the ESI source at a flow rate of 10ul/min along with the mobile phase flow rate of 500ul/min .The obtained mass spectrum showed m/z 428 as a major ion which can be attributed to the MH^+ ion of the analyte. By comparison of the Irbesartan standard MS details with Alkali degradation MS details we assumed that in presence of alkali, Base hydrolysis has been happended and Degradation impurities were formed.

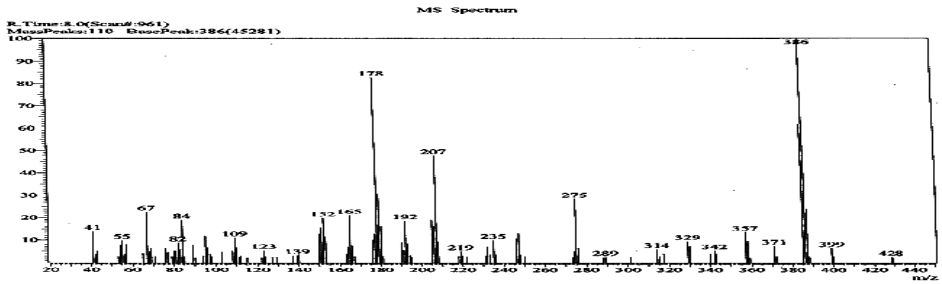

Fig. 7: Irbesartan Standard MS Spectrum

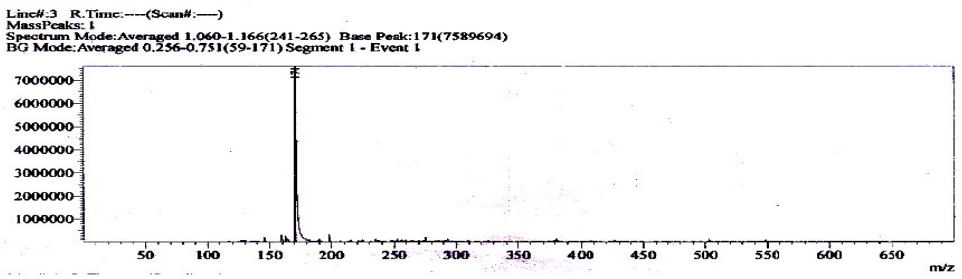

Fig. 8: Alkali degradation MS Spectrum

4.3 Peroxide degradation

Weigh 20 tablets of Irbesartan and crush the tablets. Weigh accurately the crushed sample powder equivalent to 50 mg of Irbesartan into 100 mL volumetric flask, to this add about 50 mL of diluent and sonicate for 10 minutes with occasional shaking to this add about 10 ml of 3.0% H_2O_2 and mix well. Keep on boiling water bath at 60°C for 30 minutes. Cool to room temperature and make up to the volume with diluent. Filter the supernant solution through 0.45µm GHP or finer porosity membrane filter. Injected these solutions into system and results are captured in Table-10.

4.4. Thermal degradation

Heat the Irbesartan tablets at 105°C for 72 hours. Weigh 20 tablets of Irbesartan and crush the tablets. Weigh accurately the crushed sample powder equivalent to 50 mg of Irbesartan into 100 mL volumetric flask, to this add about 50 mL of diluent and sonicate for 10 minutes with occasional shaking and make up to the volume with diluent. Filter the solution through 0.45µm GHP or finer porosity membrane filter. Injected these solutions into system and results are captured in Table-10.

4.5 UV light degradation

Expose the Irbesartan tablets to UV light at 254nm for three days. Weigh 20 tablets of Irbesartan and crush the tablets. Weigh accurately the crushed sample powder equivalent to 50 mg of Irbesartan into 100 mL volumetric flask, to this add about 50 mL of diluent and sonicate for 10 minutes with occasional shaking and make up to the volume with diluent. Filter the solution through 0.45 µm GHP or finer porosity membrane filter. Injected these solutions into system and results are captured in Table-10.

Table 10: Forced Degradation Study Results

S. No	Stress condition	Peak purity	% Degradation
1	Sample as such	0.99	---
2	Acid degradation sample (5N HCl)	1.00	16.92
3	Alkali degradation sample (5N NaoH)	1.00	25.77
4	Peroxide degradation sample (3.0% H_2O_2)	1.00	13.82
5	Heat degradation sample (105°C)	0.99	10.82
6	UV light degradation sample (254nm)	0.99	12.65

5.0 CONCLUSION

The newly developed UFLC method is validated as per ICH guidelines for the estimation of Irbesartan and Its Impurities both in active pharmaceutical ingredient and formulations. Satisfactory results were obtained for all the validation parameters. The proposed method can be used for the regular quality control analysis for the determination of Irbesartan in bulk drugs and in formulations. The stress degradation study reveals the possible impurities arised from the alkali degradation.

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