ORIGINAL ARTICLE

# A validated stability-indicating liquid chromatographic method for determination of process related impurities and degradation behavior of Irbesartan in solid oral dosage

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## ABSTRACT

The present work describes the development and validation of a stability-indicating RP-HPLC method for the estimation of degradation and process related impurities of Irbesartan, namely Impurity-1, Impurity-2, Impurity-3 and Impurity-4. The developed LC method was validated with respect to specificity, limit of detection and quantification, linearity, precision, accuracy and robustness. The chromatographic separation was achieved on Hypersil Octadecylsilyl (4.6 mm × 150 mm, 3 $\mu$m) column by using mobile phase containing a gradient mixture of solvent A (0.55% v/v ortho-phosphoric acid, pH adjusted to 3.2 with triethyl amine) and B (95:5 v/v mixture of acetonitrile and solvent A) at a flow rate of 1.2 mL/min. The detection was carried out at a wavelength of 220 nm. During method validation parameter such as precision, linearity, accuracy, specificity, limit of detection and quantification were evaluated, which remained within acceptable limits. HPLC analytical method is linear, accurate, precise, robust and specific, being able to separate the main drug from its degradation products. The degradation products were well-resolved from the main peak and its impurities, thus proving the stability-indicating power of the method. The method is stability-indicating in nature and can be used for routine analysis of production samples and to check the stability of the Irbesartan HCl tablets.

**Key words:** Degradation, high-performance liquid chromatography, irbesartan, mass balance, stability-indicating, validation

## INTRODUCTION

Present drug stability test guidance Q1A (R2) issued by International Conference on Harmonization (ICH)[1] suggest that stress studies should be carried out on a drug to establish its inherent stability characteristics, leading to identification of degradation products and hence supporting the suitability of the proposed analytical procedures. It also requires that analytical test procedures for stability samples should be stability indicating and they should be fully validated.

Irbesartan is a non-peptide compound, chemically described as a 2-butyl-3-(p-[o-1Htetrazol-5-ylphenyl] benzyl)-1,3-diazaspiro (4.4) non-1-en-4-one [Figure 1].[2] Irbesartan is an oral medication that is used to treat high blood pressure (hypertension) and diabetic nephropathy or kidney disease. It belongs to a class of drugs called angiotensin receptor blockers (ARBs). Angiotensin, formed in the blood by the action of angiotensin converting enzyme, is a powerful chemical that attaches to ARBs found in many tissues but primarily on smooth muscle cells of blood vessels. Angiotensin's attachment to the receptors causes the blood vessels to narrow (vasoconstrict), which leads to an increase in blood pressure (hypertension). Irbesartan blocks the angiotensin receptor. By blocking the action of

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angiotensin, Irbesartan dilates blood vessels and reduces blood pressure. The Food and Drug Administration approved Irbesartan in September 1997.[3]

Regulatory requirements for the identification, qualification and control of impurities in drug substances and their formulated products are now being explicitly defined, particularly through the ICH. It is also recommended by ICH that all routine impurities at or above 0.1% level, should be identified through appropriate analytical methods.[4,5]

Irbesartan and Irbesartan tablets are cited in the British pharmacopoeia and United State pharmacopoeia to have contamination by compounds A (Impurity-1) [Figure 1].[6,7] Therefore, it was thought worth determining the impurities of Irbesartan to ensure the quality, efficacy and safety of the final pharmaceutical formulation. In addition, two in-house process related impurities and Impurity-4,[8] a reported impurity, is likely to be present in formulations of irbesartan with the interaction of the polyethylene glycol.

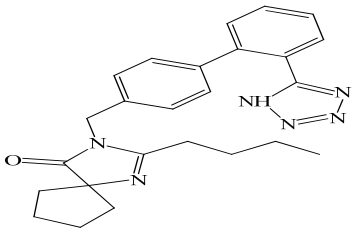
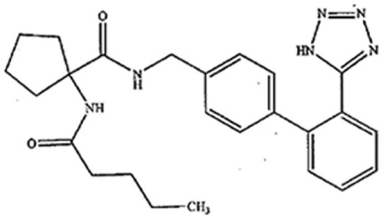
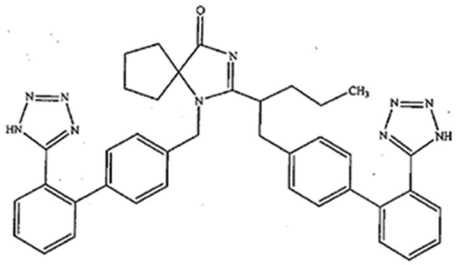
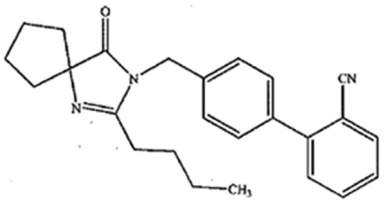
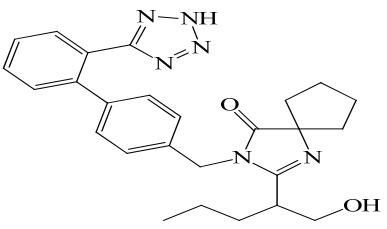
| Name | Chemical name | Chemical structure |
|---|---|---|
| Irbesartan | 2-butyl-3- ({4-[2-(2H-1,2,3,4- tetrazol-5-yl) phenyl] phenyl} methyl)-1,3-diazaspiro [4.4]non-1-en-4-one |  |
| Impurity-1 | 1-(pentanoylamino)-N- [[2′-(1H-tetrazol-5-yl) biphenyl- 4-yl] methyl] cyclopentane carboxamide or 1-pentanoylamino-cyclopentane carboxylic acid [2′-(1H-tetrazol- 5-yl)-biphenyl-4-ylmethyl]- amide |  |
| Impurity-2 | 4′-(2-(1-«2′- tetrazolylbiphenyl-4-yl) methyl)-4-oxo-1, 3diazaspiro [4.4] non-2-en-2-yl) penty1) biphenyl-2-tetrazole |  |
| Impurity-3 | 1-[(2′-Cyano biphenyl- 4-yl) methyl]-2n-butyl-4-spirocyclopentane- 2-imidazolin-5-one |  |
| Impurity-4 | 3-((2′-(2H-tetrazol-5-yl)- [1,1′-biphenyl]- 4-yl) methyl)-2-(1-hydroxypantane- 2-yl)- 1,3-diazaspiro [4.4] non-1-en-4-one |  |

**Figure 1:** Chemical structure of irbesartan and its impurities

According to the literature survey, few high-performance liquid chromatography (HPLC) and high performance thin layer chromatography assay methods have been reported for determination of Irbesartan in pharmaceutical preparation.[9-12] Estimation of Irbesartan in biological fluids using liquid chromatography with mass spectroscopy, ion spray tandem mass spectroscopy, electron spray tandem mass spectroscopy.[13-16] To the best of our present knowledge, there is no stability-indicating LC method available for the estimation of Irbesartan and its impurities in pharmaceutical formulation. Accordingly, the aim of the present study was to establish a simple stability-indicating reverse phase liquid chromatographic (RP-LC) method was developed for determination of impurities and degradation products in Irbesartan drug product, which will serve as a linear and accurate for its determination.

According to the literature survey, only few analytical methods have been reported for the quantitative estimation of Irbesartan and it's impurities, there is a necessity for investigation of new analytical methods for quantitative estimation of Irbesartan in pharmaceutical dosage form. In view of the above fact, the following analytical methods are planned to develop with high sensitivity, accuracy and precision.

The present work describes the development and validation of a stability-indicating reverse phase high-performance liquid chromatographic (RP-HPLC) method for the estimation of degradation and process related impurities of Irbesartan, namely impurity-1, impurity-2, impurity-3 and impurity-4 [Figure 1]. The developed LC method was validated with respect to specificity, limit of detection (LOD) and quantification, linearity, precision, accuracy and robustness. Forced degradation studies were performed on the placebo (all excipient mixture without Irbesartan drug substance) and drug product to show the stability-indicating nature of the method. These studies were performed in accordance with established ICH guidelines.[17,18]

## MATERIALS AND METHODS

### Reagents and chemicals

Samples of Irbesartan tablets and its impurities were supplied by Dr. Reddy's Laboratories Limited, Hyderabad, India. The HPLC grade acetonitrile, analytical grade triethylamine and orthophosphoric acid were purchased from J. T. Baker, Mumbai, India. High purity water was prepared by using Millipore Milli-Q Plus water purification system (Millipore, Milford, MA, USA).

### Equipment

The chromatography analysis was performed using waters HPLC separation module (Waters Corporation, Milford, USA) equipped with ultraviolet (UV) detector, binary solvent manager and auto sampler system. The output signals were monitored and processed using Empower 2 software. Cintex digital water bath was used for hydrolysis studies. Photo-stability studies were carried out in the photo-stability chamber (Sanyo, Leicestershire, UK). Thermal stability studies were performed in a dry air oven (Cintex, Mumbai, India). The pH of the solutions was measured by a pH meter (Mettler-Toledo, Switzerland).

### Chromatographic conditions

The method was developed using hypersil, ODS, C18 (150 mm × 4.6 mm) 3 µm with mobile phase containing a gradient mixture of solvent A (0.55% v/v orthophosphoric acid, pH adjusted to 3.2 with triethylamine) and solvent B (mixture of solvent A and acetonitrile in the ratio of 5:95 v/v, respectively). The gradient program (T/%B) was set as 0/40, 10/40, 22/50, 26/50, 28/40 and 35/40. The flow rate of the mobile phase was set at 1.2 mL/min. The column temperature was maintained at 25°C and the eluted compounds were monitored at the wavelength of 220 nm. The injection volume was 10 µl.

### Preparation of standard solution

Stock solution of Irbesartan was prepared in diluent with a concentration of 200 µg/mL. Working standard solution was prepared from diluting above stock solution of Irbesartan with the final concentration of 2 µg/mL.

### Preparation of sample solution

Twenty ($n$ = 20) tablets were weighed and the tablets were transferred into a clean, dry mortar. Tablets powder equivalent to 100 mg of Irbesartan was dissolved in diluent with sonication for about 30 min to prepare a solution containing 400 µg/mL drugs. This solution was centrifuged at 10,000 rpm for about 10 min.

### Forced degradation studies

Specificity is the ability of the method to measure the analyte response in the presence of its potential impurities. The specificity of the developed LC method for Irbesartan was carried out in the presence of its impurities and degradation products. Stress studies were performed at 400 µg/mL concentration of Irbesartan on tablets to provide an indication of the stability-indicating property and specificity of proposed method. All the solutions used in forced degradation studies were prepared by dissolving the drug product in small volume of stressing agents. After degradation, these solutions were diluted with diluent to yield stated Irbesartan concentration of about 400 µg/mL.

The stress condition employed for degradation study included acid hydrolysis (5 N HCl at 70°C for 15 h), base hydrolysis (5 N NaOH at 70°C for 5 h), oxidation (3% $H_2O_2$ at 40°C for 6 h), hydrolytic (water at 70°C for 15 h), thermal (105°C for 15 h), humidity (25°C/90% RH for 7 days) and photolytic degradation (drug product exposed to visible light for 240 h resulting in an overall illustration 1.2 million

lux h and UV light for 250 h resulting an overall illustration 200 W h/m$^2$ at 25°C.[19] The purity of the peaks obtained from the stressed samples was verified by using the photodiode array (PDA) detector. The purity angle was within the purity threshold limit obtain in the all the stressed samples and demonstrate the analyte peak homogeneity.

## RESULTS AND DISCUSSION

### Method development and optimization of stability-indicating HPLC method

The important criteria for the development of the successful RP-HPLC method for the determination of Irbesartan-related substances in tablet dosage form, was the method which should be able to determine all impurities of the drug in a single run with a good amount of resolution. The method should be accurate, reproducible, robust, stability-indicating, free from interference (blank/placebo/other unknown degradation product) and straightforward enough for routine use in quality control laboratories. The main objective of the chromatographic method development was to separate Irbesartan impurities from the main peak with a good amount of resolution. The initial method development started with an Isocratic mobile phase. Different combination of buffers: Acetonitrile in the range of 90:10-10:90 v/v were used and it was observed that the impurity-2 and impurity -1 are mostly polar in nature, whereas impurity-3 is non-polar in nature. Then an increase in the buffer concentration of more than 50% in the mobile phase lead to more retention of impurity-3 on the column, which lead to an increased run time of more than 60 min. Furthermore, the peak shape of impurity-3 is not proper. By a decrease in buffer concentration to less than 50% in the mobile phase, retention of IBE impurity was reduced, but the resolution between the impurity-2 and impurity -1 also decreased, where impurity-2 peaks eluted to nearly a void volume. As a result to increase the resolution and baseline stabilization, the gradient mobile phases were switched, where modified buffer A (0.55% v/v orthophosphoric acid, pH adjusted to 3.2 with triethylamine) and solvent B (mixture of buffer A and acetonitrile in the ratio of 5:95 v/v, respectively) and hypersil, ODS, C18 (150 mm × 4.6 mm) 3 µm column. Different gradient programs have been attempted to improve the run time to be less than 60 min with good retention of the impurity-2 and impurity -1 on the column. The acidic stressed sample and impurity-spiked sample were injected in the column to check for good resolution between the known and unknown impurities and Irbesartan [Table 1].

During the optimization of the method, the chromatographic condition has been finalized as hypersil, ODS, C18 (150 mm × 4.6 mm) 3 µm particle size column was used as stationary phase. The mobile phase A consisted of 0.55%v/v orthophosphoric acid, pH adjusted to 3.2 with triethylamine and mobile phase B contained a mixture of mixture of solvent A and acetonitrile in the ratio of 5:95 v/v, respectively. The gradient program (T/%B) was set as 0/40, 10/40, 22/50, 26/50, 28/40 and 35/60. The flow rate of the mobile phase was set at 1.2 mL/min. The column temperature was maintained at 25°C and the eluted compounds were monitored at the wavelength of 220 nm. The injection volume was 10 µl.

### Analytical parameters and validation

The optimized chromatographic conditions were validated by evaluating specificity, linearity, precision, accuracy, LOD, limit of quantification (LOQ), robustness and system suitability in accordance with ICH guidelines Q2 (R1).[12,13]

### Specificity

The specificity of a method is its suitability for the analysis of a substance in the presence of potential impurities. Stress testing of a drug substance can help to identify likely degradation products, which can help to establish degradation pathways and the intrinsic stability of the molecule. It can also be used to validate the stability-indicating power of the analytical procedures used. The specificity of the LC method for Irbesartan has been determined in the presence of four impurities [Figure 2].

### Forced degradation study of drug product

The stress degradation study was performed on the drug product, which includes acid hydrolysis (5 N HCl at 70°C for 15 h), base hydrolysis (5 N NaOH at 70°C for 5 h), oxidation (3% $H_2O_2$ at 40°C for 6 h), hydrolytic (water at 70°C for 15 h), thermal (105°C for 15 h), humidity (25°C/90% RH for 7 days) and photolytic degradation (drug product exposed to visible light for 240 h resulting in an overall illustration 1.2 million lux h and UV light for 250 h resulting an overall illustration 200 watt h/m$^2$ at 25°C. The stress study was performed as per the ICH recommendation.[19] Peak purity was checked for the Irbesartan peak by using a PDA detector in stress samples. An assay of stressed samples was performed for comparison to the reference standard and the mass balances (% assay + % impurities + % degradation products) were then calculated. No peaks were found at the retention time of Irbesartan and its four impurities in blank and placebo chromatograms, which proves there was no interference from the blank and placebo. Slight degradation was observed when the drug product was subjected to acid hydrolysis and basic stress conditions and was stable in photolytic and humidity stress conditions.

**Table 1: Chromatographic performance data**

| Parameters | Acceptance criteria | Observed value | |
|---|---|---|---|
| | | Precision (day-1) | Intermediate precision (day-2) |
| Resolution | ≥3.0 | 1.0 | 1.0 |
| Area ratio | ≥0.9 and ≤1.1 | 7.8 | 6.9 |
| USP plate count | >3000 | 13052 | 11798 |
| USP tailing | <2.0 | 1.0 | 1.0 |

USP: United states pharmacopoeia

Irbesartan was sensitive in basic and acidic conditions and it significantly degraded into the impurity -1 [Figures 3 and 4]. Peak purity test results from the PDA detector confirmed that the Irbesartan peak obtained from all of the stress samples analyzed was homogeneous and pure. Peak purity results from the PDA detector for the peaks produced by the degradation of Irbesartan, confirmed that all these peaks were homogeneous and pure for all the stress samples analyzed [Table 2]. The mass balance for the stressed samples was close to 97% [Table 2]. The assay of Irbesartan was unaffected by the presence of the impurities/degradation products, confirming the stability-indicating power of the method.

The LOD and LOQ for Irbesartan and its impurities were determined at a signal-to-noise ratio of 3:1 and 10:1, respectively, by injecting a series of dilute solutions with known concentrations. Precision study was also carried out at the LOQ level by injecting six individual preparations and calculating the % relative standard deviation (RSD) of the area [Table 3].

## Linearity of response

Solutions for testing the linearity of the related substances were prepared by diluting the impurity stock solution to five different concentrations from the LOQ to 150% of the permitted maximum level of the impurity. The correlation coefficients, slopes and y-intercepts of the calibration plots are reported. Calibration plots for the five related substances were linear over the ranges tested. The correlation coefficients were >0.999 for all of the components [Table 3]. These results show that there was an excellent correlation between the peak area and concentration for the five impurities.

## Precision

The precision of the method was verified by repeatability and intermediate precision. Repeatability was checked by injecting five individual preparations of the real sample of Irbesartan spiked with 0.30% of its four impurities. The intermediate precision of the method was also evaluated using a different analyst and a different instrument and performing the analysis on a different day. %RSD of area

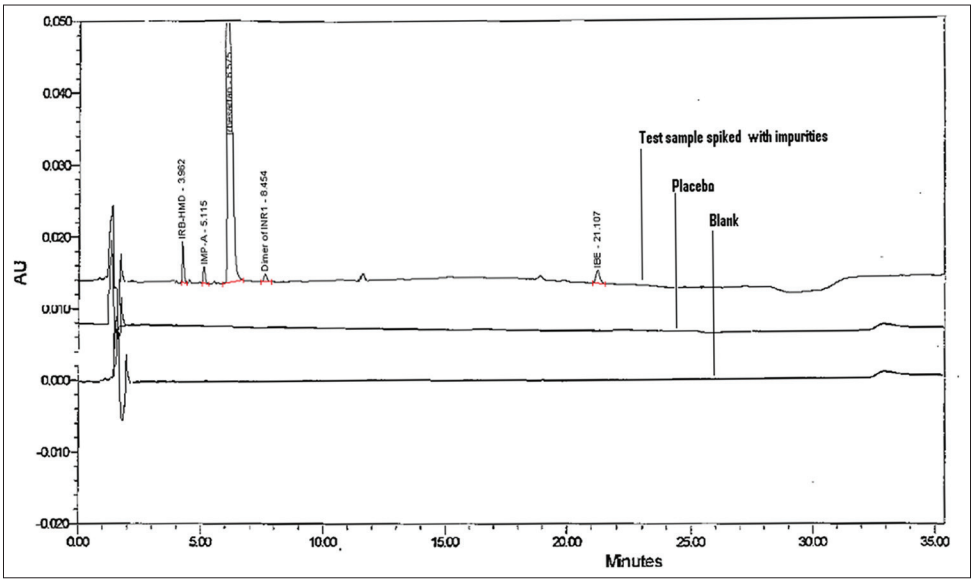



**Figure 2:** Typical high-performance liquid chromatography chromatogram placebo, blank and sample solution spiked with impurities

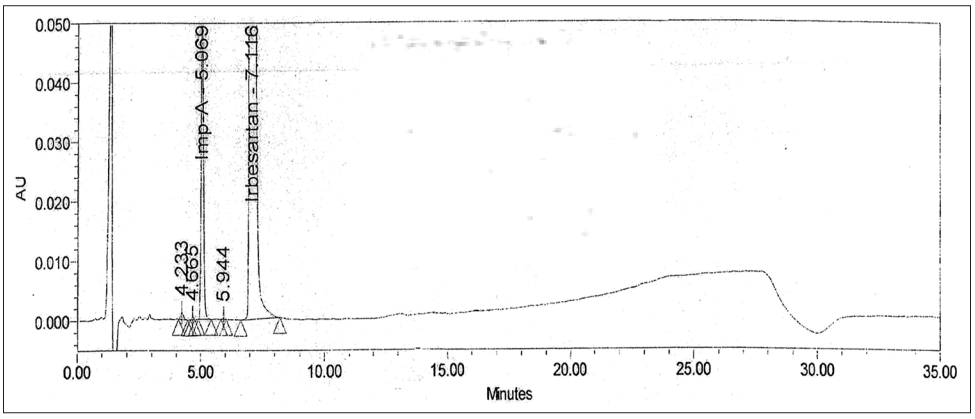



**Figure 3:** Liquid chromatography chromatogram obtain from force degradation study of pharmaceutical solid sample solution in acidic condition

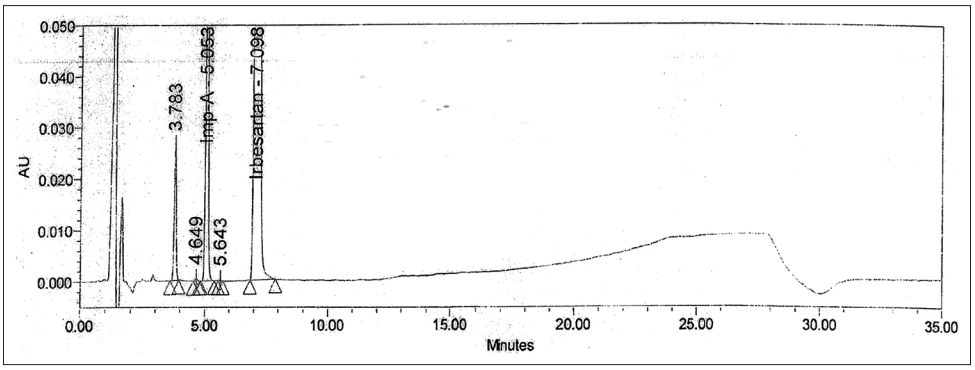



**Figure 4:** Liquid chromatography chromatogram obtain from force degradation study of pharmaceutical solid sample solution in basic condition

**Table 2: Stress testing (forced degradation) data of Irbesartan**

| Stress condition | % Impurity-1 | % Impurity-2 | % Impurity-3 | % Impurity-4 | % degradation | Mass balance (%) |
|---|---|---|---|---|---|---|
| Unstressed sample | 0.047 | Below LOQ | Below LOQ | Below LOQ | NA | NA |
| Acid hydrolysis | 2.84 | Below LOQ | Below LOQ | Below LOQ | 4.0843 | 99 |
| Base hydrolysis | 4.19 | Below LOQ | Below LOQ | Below LOQ | 6.5928 | 97 |
| Oxidation degradation | 0.029 | Below LOQ | Below LOQ | Below LOQ | 0.4027 | 97 |
| Thermal degradation | 0.042 | Below LOQ | Below LOQ | Below LOQ | 0.0142 | 100 |
| Water degradation | 0.07 | Below LOQ | Below LOQ | Below LOQ | 0.0118 | 99 |
| Photolytic degradation | 0.065 | Below LOQ | Below LOQ | Below LOQ | 0.0076 | 102 |
| Humidity degradation | 0.052 | Below LOQ | Below LOQ | Below LOQ | Nil | 103 |

LOD: Limit of detection, LOQ: Limit of quantification

**Table 3: Evaluation of precision, intermediate precision, LOD, LOQ and linearity data**

| Parameter | % Impurity-1 | Impurity-2 | Impurity-3 | Impurity-4 | Irbesartan |
|---|---|---|---|---|---|
| LOD (µg/mL) | 0.004 | 0.007 | 0.003 | 0.008 | 0.004 |
| LOQ (µg/mL) | 0.012 | 0.022 | 0.014 | 0.025 | 0.011 |
| Correlation coefficient | 0.998 | 0.998 | 0.999 | 1.000 | 0.998 |
| Intercept (a) | 423.1479 | 226.3880 | 704.2949 | 179.194 | 2218.6784 |
| Slope (b) | 26735.61 | 18789.32 | 39347.40 | 24328.073 | 28402.42 |
| Bias at 100% response | 3 | 2 | 3 | 0.413 | 4 |
| Precision (% RSD) | 4.7 | 3.8 | 2.5 | 1.96 | 2.9 |
| Intermediate precision (% RSD) | 2.2 | 4.4 | 4.8 | 0.7 | 2.5 |
| Precision at LOQ (% RSD) | 3.4 | 6.4 | 7.7 | 5.48 | 8.4 |

LOD: Limit of detection, LOQ: Limit of quantification, RSD: Relative standard deviation

for each impurity was calculated for both precision as well as intermediate precision and was found to be within 2%. These results confirmed the precision and ruggedness of the method [Table 3].

## Accuracy

Accuracy of the method for Irbesartan and its impurities were evaluated in triplicate using six concentration levels of LOQ, 50%, 75%, 100%, 130% and 150%. The percentage recoveries for each impurity were calculated [Table 4].

## Robustness

To determine the robustness of the developed method, experimental conditions were deliberately altered and the resolution between impurity-2 and Irbesartan and system suitability parameters for Irbesartan standard were evaluated. In order to study the effect of flow rate on resolution, it was changed to 1.0 and 1.4 mL/min. The effect of pH was studied at pH 3.0 and 3.3. The effect of column temperature was studied at 25 and 30°C. In all these experiments, the mobile phase components were not changed. The effect of the percent organic strength on the resolution was studied by varying acetonitrile by -10 to +10% while other mobile phase components were held constant. In all of the deliberately varied chromatographic conditions, the selectivity as well as the performance of the method were unchanged, which proves the robustness of the method [Table 5].

## Stability in solution and in the mobile phase

No significant changes in the amounts of the five impurities

**Table 4: Results from evaluation of the accuracy of the liquid chromatographic method**

| Spiked level[a] | % recovery[b] | | | |
|---|---|---|---|---|
| | % impurity-1 | impurity-2 | impurity-3 | Impurity-4 |
| LOQ | 108.3±0.1 | 96.7±7.8 | 104.2±0.1 | 102.5±4.2 |
| 50% | 97.8±3.9 | 99.5±2.2 | 101.9±7.9 | 98.7±2.0 |
| 100% | 100±1.1 | 98.6±1.8 | 99.1±0.5 | 98.6±2.1 |
| 130% | 98.8±3.6 | 97.1±3.7 | 98.5±3.2 | 96.4±1.2 |
| 150% | 97.7±1.0 | 97.5±0.7 | 97.3±0.3 | 98.1±1.4 |

[a]Spiked level of four impurities spiked with respect to specification level, [b]Mean±% RSD for three determinations, LOQ: Limit of quantification, RSD: Relative standard deviation

**Table 5: Results from evaluation of robustness study of the liquid chromatographic method**

| Variation in chromatographic condition | Observed system suitability parameters | | | |
|---|---|---|---|---|
| | Area ratio | USP tailing | USP plate count | USP resolution |
| Acceptance criteria | ≥0.9 and ≤1.1 | <2.0 | >3000 | ≥3.0 |
| Column-1 | 1.0 | 1.0 | 13052 | 7.8 |
| Column-2 | 1.0 | 1.0 | 11798 | 6.9 |
| Column temperature 20°C | 1.0 | 1.2 | 15347 | 5.6 |
| Column temperature 30°C | 1.0 | 1.1 | 16551 | 3.5 |
| Flow rate 1.0 mL/min | 1.0 | 1.2 | 16570 | 5.4 |
| Flow rate 1.4 mL/min | 1.0 | 1.1 | 14591 | 5.4 |
| Mobile phase-A 90% | 1.0 | 1.1 | 15445 | 4.2 |
| Mobile phase-A 110% | 1.0 | 1.1 | 15487 | 3.7 |
| Mobile phase buffer pH 3.0 | 1.0 | 1.2 | 15367 | 8.5 |
| Mobile phase buffer pH 3.3 | 1.0 | 1.2 | 15286 | 3.7 |

USP: United states pharmacopoeia

were observed during the solution stability and mobile phase stability experiments when performed using the related substances method. The results from the solution stability and mobile phase stability experiments confirmed that standard solutions and samples were stable for up to 24 h during the determination of related substances. The mobile phase was stable up to 48 h.

## CONCLUSION

This research paper describes the A simple and efficient RP-HPLC method development and validation were discussed. The method was found to be precise, accurate, linear, robust and rugged during validation. The method is stability-indicating and can be used for routine analysis of production samples and to check the stability of the Irbesartan HCl tablets.

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