STABILITY INDICATING METHOD DEVELOPMENT AND VALIDATION OF FIMASARTAN BY REVERSE-PHASE HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY IN BULK AND PHARMACEUTICAL DOSAGE FORM

SRUTHI A*, UTTAM PRASAD PANIGRAHY

Department of Pharmaceutical Analysis, CMR College of Pharmacy, Hyderabad, Telangana, India. Email: uttamanigrahy@gmail.com

Received: 23 October 2020, Revised and Accepted: 2 December 2020

ABSTRACT

Objective: A rapid, sensitive and specific reverse phase High Performance liquid Chromatography (RP-HPLC) method was developed for the estimation of Fimasartan in bulk and pharmaceutical dosage form.

Method: The RP-HPLC analysis was performed isocratically on a Primacel C18 column (150 mm × 4.6 mm internal diameter, 5 μm particle size) using mobile phase of composition Acetonitrile and 0.1% orthophosphoric Acid in 80:20, v/v proportions with a flow rate of 0.8 ml/min.

Results: The analyte was monitored with UV-detector at 265 nm. In the developed method Fimasartan elutes at a typical retention time of 2.4 min. The proposed method is having linearity in the concentration ranging from 5-30 μg/ml of Fimasartan.

Conclusion: The method was statistically validated and had been applied to analysis of the drug in bulk and pharmaceutical dosage form.

Keywords: Fimasartan, Reverse-phase high-performance liquid chromatography, C18 column.

INTRODUCTION

Fimasartan is a typical anti-hypertensive agent. Fimasartan acts on the kidney’s rennin-angiotensin cascade, which begins when renin release from the kidney causes the breakdown of angiotensinogen into angiotensin I. In blocking the AT1 receptor, Fimasartan inhibits vasoconstriction favoring vasodilation. Fimasartan is chemically known as 2-[2-butyl-4-methyl-6-oxo-1-[4-[2-(2H-tetrazol-5-yl) phenyl] phenyl] methyl] pyrimidin-5-yl]-N and N-dimethylthianethioamide shown in Fig. 1.

Literature survey reveals the availability of few methods such as ultraviolet (UV), high-performance liquid chromatography (HPLC), and LC-MS in biological fluids and pharmaceutical dosage forms [1-16]. The present method gives the accurate information regarding method development and validation of Fimasartan in bulk and pharmaceutical dosage form using UV detector at 265 nm which is simple, accurate, economic, rapid, reproducible, and sensitive according to procedures and acceptance criteria based on FDA guidelines and recommendations of ICH.

METHODS

Chemical and reagents

Fimasartan was procured as gift sample from Metrochem Pvt. Ltd, Hyderabad, India. Fimasartan® 120 mg (formulation) was manufactured by Ajanta Pharma Limited, HPLC grade acetonitrile, HPLC grade water, and orthophosphoric acid were obtained from Merck, Hyderabad, India. All other chemical reagents used were of analytical grade.

Selection of wavelength

Wavelength was selected by dissolving Fimasartan in suitable solvent (acetonitrile) and the resulting solution was scanned in UV region, that is, 200–400 nm. Fimasartan has showed that maximum absorption at 265 nm was selected shown in Fig 2.

Chromatographic conditions

A Shimadzu HPLC was used for the analysis of the entire method. The method was carried out on Primacel C18 (150 mm × 4.6 mm i.d., 5 μm) column as a stationary phase and Acetonitrile:0.1% OPA (80:20,v/v) as the mobile phase at a flow rate of 0.6 ml/min. Rheodyne injector with 25 μl loop was used for injecting the samples. Finally, the sample was analyzed at 265 nm and the mobile phase was sonicated filtered and degassed.

Preparation of mobile phase

Acetonitrile and 0.1% OPA in the ratio of 80:20 v/v were used as a mobile phase for present study which is prepared by dissolving 80 ml of acetonitrile and 20 ml of 0.1% OPA in a reservoir. 0.1% orthophosphoric acid was prepared by accurately measuring of 0.1 ml of OPA and dissolving in 100 ml of HPLC grade water. The above mobile phase prepared is sonicated and degassed.

Preparation of standard solution

Standard solution was prepared by accurately weighing 100 mg of Fimasartan and transferring into 100 ml volumetric flask. To this add few ml of acetonitrile and dissolve the drug properly. Finally make up the solution to 100 ml with acetonitrile (1000 μg/ml).

Preparation of sample solution

Tablet powder equivalent to 100 mg of Fimasartan was accurately weighed and transferred into 100 ml volumetric flask and make up the volume to 100 ml with acetonitrile. Sonicate the solution for about 15 min and filter the solution through Whatman filter paper (No. 1) into another 100 ml volumetric flask (1000 μg/ml). The solution was further diluted with the diluent to the working concentration range of calibration curve.

Calibration curve

Ten milliliters of standard solution were transferred into 100 ml volumetric flask and the volume was made up to 100 ml using acetonitrile (100 μg/ml). From this solution, further dilutions were made in the concentration range of 5 μg/ml–30 μg/ml. Further these concentrations were injected thrice into the system and the calibration curve was constructed by plotting concentration on X-axis and peak area on Y-axis.
Assay procedure for the commercial formulation
Fimasartan is available as film coated tablets containing equivalent amount of Fimasartan potassium trihydrate. Fimasartan is available in the local market with brand names FIMANTA (120 mg, Ajanta Pharma Limited, India). 1000 μg/ml of sample solution which was prepared and further diluted to 10 μg/ml and was injected into HPLC system and the % assay was calculated and the values are given in Table 1.

RESULTS AND DISCUSSION
Specificity
The blank prepared from the formulation excipients was injected into the system. No peaks were detected in the retention time corresponding to analyte peak, which indicates that no interference of excipients of the formulation which indicates that the method developed is having the specificity. The standard and blank chromatogram is given in Fig. 3.

Linearity
Ten milliliters of standard solution were transferred into 100 ml volumetric flask and the volume was made up to 100 ml using acetonitrile (100 μg/ml). From this solution, further dilutions were made in the concentration range of 5 μg/ml-30 μg/ml. Further these concentrations were injected thrice into the system and the calibration curve was constructed by plotting concentration of Fimasartan on X-axis and mean peak area on Y-axis. The method is having good linearity ($r^2 = 0.9995$). The linearity graph and table were given in Table 2 and Fig. 4.

Limit of detection (LOD)
This is the smallest concentration of analyte which can be detected. This can be calculated using the following formula:

\[
\text{LOD} = 3.3 \times \text{Standard deviation/slope}
\]

By calculating, it was found as 1.3 μg/ml.

Table 1: Assay of tablet formulation

| Drug   | Fimanta @tablet label claim (mg) | Amount found (mg) | % Label claim±% RSD (n=3) |
|--------|---------------------------------|------------------|--------------------------|
| Fimasartan | 120                             | 119.95           | 99.96±0.13               |

Table 2: Linearity table of Fimasartan

| Concentration (μg/ml) | Peak area (mV) |
|-----------------------|----------------|
| 5                     | 317.684        |
| 10                    | 625.400        |
| 15                    | 894.706        |
| 20                    | 1176.303       |
| 25                    | 1476.828       |
| 30                    | 1749.634       |

Fig. 1: Chemical structure of Fimasartan

Fig. 2: Ultraviolet spectra of Fimasartan

Fig. 3: Blank and standard chromatogram of Fimasartan
**Limit of quantification (LOQ)**
This is the lowest concentration of analyte which can be quantified. This can be calculated using the following formula:

\[ \text{LOQ} = 10 \times \frac{\text{Standard deviation}}{\text{slope}} \]

By calculation it was found as 4 µg/ml.

**Accuracy**
It is an agreement between the true value and the measured value. Accuracy is performed by injecting 50%, 100%, and 150% levels for 3 times into HPLC system. Finally, the amount found, amount added, %recovery, mean recovery, %SD, and %RSD were calculated and are clearly illustrated in Table 3 which indicates that the obtained results are in good agreement between each other.

**Precision**

**Repeatability**
System precision
This is performed by injecting 10 µg/ml of standard solution 6 times into HPLC system note down the peak areas and calculates the average, SD, and %RSD which is clearly illustrated in Table 4 and Fig. 5.

**Method precision**
This is performed by injecting 10 µg/ml of sample solution six times into HPLC system note down the peak areas and calculates the %assay, average, SD, and %RSD which is clearly illustrated in Table 5 and Fig. 6.

**Intermediate precision/Ruggedness**
It is performed on two different days and by two different analysts and in two different labs by maintaining the same conditions within the laboratories was shown in (Fig. 7).

Analyst-1: Inject the 100% concentration of sample (i.e., 10 µg/ml) for 6 times into HPLC system and note down the area for each and every injection and calculate the SD and % RSD values which is clearly illustrated in Table 6.

Analyst-2: Inject the 100% concentration of sample (i.e., 10 µg/ml) for 6 times into HPLC system and note down the area for each and every injection and calculate the SD and % RSD values which is clearly illustrated in Table 6.

Day-1: Inject the 100% concentration of sample (i.e., 10 µg/ml) for 6 times into HPLC system and note down the area for each and every injection and calculate the SD and % RSD values which is clearly illustrated in Table 6.

Day-2: Inject the 100% concentration of sample (i.e., 10 µg/ml) for 6 times into HPLC system and note down the area for each and every injection and calculate the SD and % RSD values which is clearly illustrated in Table 6.

**Reproducibility**
This is defined as the precision between the labs. It is performed by injecting 100% concentration of sample (i.e., 10 µg/ml) for 6 times into two different HPLC system in two different laboratories and note down the area for each and every injection and calculate the SD and % RSD values which is clearly illustrated in Table 7 and Fig. 8.

### Table 3: Results showing accuracy of Fimasartan

| Level (%) | Amount added (µg/ml) | Amount found (µg/ml) | % Recovery | % Avg recovery | % SD | %RSD |
|-----------|---------------------|----------------------|------------|----------------|-----|------|
| 50        | 5                   | 4.98                 | 99.6       | 99.6           | 0.2 | 0.200 |
| 50        | 5                   | 4.97                 | 99.4       |                |     |      |
| 100       | 10                  | 9.97                 | 99.7       | 99.7           | 0.1 | 0.100 |
| 100       | 10                  | 9.96                 | 99.6       |                |     |      |
| 100       | 10                  | 9.98                 | 99.8       |                |     |      |
| 150       | 15                  | 14.95                | 99.6       | 99.70          | 0.173 | 0.173 |
| 150       | 15                  | 14.94                | 99.6       |                |     |      |
| 150       | 15                  | 14.95                | 99.6       |                |     |      |

### Table 4: Results showing system precision values of Fimasartan

| Concentration (µg/ml) | Retention time | Peak area (mV) | Average peak area (mV) | SD   | %RSD |
|-----------------------|----------------|----------------|------------------------|------|------|
| 10                    | 2.4            | 625.410        | 626.33                 | 1.34 | 0.21 |
| 10                    | 2.4            | 626.675        |                        |      |      |
| 10                    | 2.4            | 625.054        |                        |      |      |
| 10                    | 2.4            | 628.253        |                        |      |      |
| 10                    | 2.4            | 627.430        |                        |      |      |
| 10                    | 2.4            | 625.138        |                        |      |      |

### Table 5: Results showing method precision values of Fimasartan

| Concentration (µg/ml) | Retention time | Peak area (mV) | %Assay | Average %Assay | S. D  | %RSD |
|-----------------------|----------------|----------------|--------|----------------|-------|------|
| 10                    | 2.4            | 627.497        | 100.10 | 99.96          | 0.120 | 0.120|
| 10                    | 2.4            | 626.364        | 99.90  |                |       |      |
| 10                    | 2.4            | 625.443        | 99.81  |                |       |      |
| 10                    | 2.4            | 627.184        | 100.00 |                |       |      |
| 10                    | 2.4            | 626.287        | 99.90  |                |       |      |
| 10                    | 2.4            | 627.360        | 100.10 |                |       |      |
It is defined as a small or deliberate change in parameter should not affect any method. This is performed by change in flow rate (± 10%) and mobile phase (± 10%).

**Change in flow rate**

This is performed by changing the flow rate of ± 10% (i.e., 0.7 ml/min and 0.9 ml/min). Inject the 100% concentration, that is, 10 μg/ml six 6 times for both the flow rates, that is, 0.7 ml/min and 0.9 ml/min. Note down the peak area and calculate the %assay, average, SD, and %RSD for both the flow rates which is clearly illustrated in Table 8 and Figs. 9 and 10.

**Change in mobile phase (+10% organic phase)**

This is performed by changing the organic phase proportion of ± 10% (i.e., 88:12 v/v and 72:28 v/v). Inject the 100% concentration, that is, 10 μg/ml 6 times for both the mobile phase proportions, that is, 88:12 v/v and 72:28 v/v. Note down the peak area and calculate the %Assay, Average, SD, and %RSD for both the mobile phase proportions which is clearly illustrated in Table 9 and Figs. 11 and 12.

**Solution stability**

This is performed for 0 h, 24 h, and 48 h. Inject the 100% concentration, that is, 10 μg/ml for 6 times at 0 h, 24 h, and 48 h. Note down the peak area and calculate the %assay, average, SD, and %RSD for both the mobile phase proportions which is clearly illustrated in Table 10 and Figs. 13-15.

**Force degradation studies**

This includes acid degradation, alkali degradation, oxidative degradation, photolytic degradation, and thermal degradation which are clearly illustrated in Table 11 and Figs. 16-20.
### Table 8: Results showing change in flow rate values of Fimasartan

| Conc. (μg/ml) | Flow rate (0.7 ml/min) | Flow rate (0.9 ml/min) |
|---------------|------------------------|------------------------|
|               | Rt (mins)              | Peak area (mV)         | %Assay | Conc. (μg/ml) | Rt (mins) | Peak area (mV) | %Assay |
| 10            | 2.7                    | 625.767                | 99.81  | 10            | 2.1       | 625.296        | 99.61  |
| 10            | 2.7                    | 623.134                | 99.41  | 10            | 2.1       | 623.590        | 99.51  |
| 10            | 2.7                    | 624.620                | 99.61  | 10            | 2.1       | 625.337        | 99.71  |
| 10            | 2.7                    | 624.178                | 99.61  | 10            | 2.1       | 625.176        | 99.71  |
| 10            | 2.7                    | 623.111                | 99.41  | 10            | 2.1       | 624.659        | 99.61  |
| 10            | 2.7                    | 625.376                | 99.71  | 10            | 2.1       | 623.535        | 99.51  |
| Mean          |                        | 624.381                | 99.61  | Mean          |           | 624.324        | 99.61  |
| SD            | 0.16                   | 624.446                | 99.61  | SD            | 0.18      | 624.659        | 99.61  |
| %RSD          | 0.147                  | 624.659                | 99.61  | %RSD          | 0.052     | 624.659        | 99.61  |

### Table 9: Results showing change in mobile phase values of Fimasartan

| Conc. (μg/ml) | Flow rate −10% | Flow rate +10% |
|---------------|----------------|----------------|
|               | Rt (mins)      | Peak area (mV) | %Assay | Rt (mins)      | Peak area (mV) | %Assay |
| 10            | 2.3            | 625.767        | 99.81  | 10            | 2.6            | 624.924        | 99.81  |
| 10            | 2.3            | 625.376        | 99.71  | 10            | 2.6            | 625.176        | 99.71  |
| 10            | 2.3            | 624.178        | 99.61  | 10            | 2.6            | 625.376        | 99.71  |
| 10            | 2.3            | 623.111        | 99.41  | 10            | 2.6            | 625.376        | 99.71  |
| Mean          |                | 624.381        | 99.61  | Mean          |                | 624.324        | 99.61  |
| SD            | 0.147          | 624.446        | 99.61  | SD            | 0.052          | 624.659        | 99.61  |
| %RSD          | 0.148          | 624.659        | 99.61  | %RSD          | 0.052          | 624.659        | 99.61  |

### Table 10: Results showing solution stability values of Fimasartan

| Concentration (μg/ml) | Retention time (mins) | Peak area (mV) | %Assay | 24 h | Peak area (mV) | %Assay | 48 h | Peak area (mV) | %Assay |
|-----------------------|-----------------------|----------------|--------|------|----------------|--------|------|----------------|--------|
| 10                    | 2.4                   | 625.405        | 99.81  | 624.924        | 99.81  | 625.324        | 99.51  |
| 10                    | 2.4                   | 627.537        | 99.10  | 624.785        | 99.81  | 625.510        | 99.81  |
| 10                    | 2.4                   | 624.381        | 99.61  | 623.607        | 99.51  | 624.462        | 99.61  |
| 10                    | 2.4                   | 628.216        | 99.20  | 624.324        | 99.61  | 623.180        | 99.41  |
| 10                    | 2.4                   | 626.422        | 99.91  | 625.924        | 99.81  | 624.989        | 99.71  |
| Mean                  |                       | 625.979        | 99.51  | Mean           | 623.170        | 99.41  | 625.917        | 99.81  |
| SD                    | 0.32                  |                | 0.18   | SD             |                | 0.16   | %RSD           | 0.16   |
| %RSD                  | 0.32                  | %RSD           | 0.18   | %RSD           | 0.16   | %RSD           | 0.16   |

### Table 11: Results showing forced degradation values of Fimasartan

| Degradation parameter (n=3) | Concentration (μg/ml) | Peak area (mV) | Average peak area (mV) | %Degraded | %Recovered |
|-----------------------------|-----------------------|----------------|------------------------|-----------|-----------|
| Acid                        | 10                    | 795.442        | 794.98                 | 27.2      | 72.8      |
|                            | 10                    | 794.251        |                        |           |           |
|                            | 10                    | 795.254        |                        |           |           |
| Alkali                      | 10                    | 698.982        | 698.25                 | 11.6      | 88.4      |
|                            | 10                    | 697.251        |                        |           |           |
|                            | 10                    | 698.523        |                        |           |           |
| Peroxide                    | 10                    | 983.123        | 982.83                 | 57.1      | 42.9      |
|                            | 10                    | 982.145        |                        |           |           |
|                            | 10                    | 983.251        |                        |           |           |
| Thermal                     | 10                    | 624.252        | 624.54                 | 0.14      | 99.86     |
|                            | 10                    | 625.124        |                        |           |           |
|                            | 10                    | 625.231        |                        |           |           |
| Photolytic                  | 10                    | 625.124        | 625.16                 | 0.04      | 99.96     |
|                            | 10                    | 625.145        |                        |           |           |

### Preparation of solutions

- **Preparation of 0.1N HCl (for acid degradation)**
  Pipette out 0.812 ml of HCl in a 100 ml volumetric flask and make up the volume to 100 ml with distilled water (0.1N).

- **Preparation of 0.1N NaOH (for alkali degradation)**
  Accurately weigh 0.4 g of sodium hydroxide pellets and transfer into a 100 ml volumetric flask and make up the volume to 100 ml with distilled water (0.1N).
Fig. 7: Intermediate precision peak of Fimasartan

Fig. 8: Reproducibility peak of Fimasartan

Fig. 9: Peak which was eluted at 0.7 ml/min of flow rate

Fig. 10: Peak which was eluted at 0.9 ml/min of flow rate

Fig. 11: Peak which was eluted at +10% of mobile phase

Fig. 12: Peak which was eluted at −10% of mobile phase
Fig. 13: Peak which was eluted at 0 h

Fig. 14: Peak which was eluted at 24 h

Fig. 15: Peak which was eluted at 48 h

Fig. 16: Peak showing acid degradation

Fig. 17: Peak showing alkali degradation
c. Preparation of 3% \( \text{H}_2\text{O}_2 \) (for oxidative studies)

Pipette out 3 ml of \( \text{H}_2\text{O}_2 \) into a 100 ml volumetric flask and make up the volume to 100 ml with distilled water (3%).

**Procedure for FDS studies**

a. Acid degradation studies

From 100 \( \mu \text{g/ml} \) of stock solution of Fimasartan pipette out 1 ml to this add 1 ml of 0.1 N HCl finally make up the solution to 10 ml with ACN and keep it for 60 min and check the peak area by injecting the sample into HPLC system using the optimized mobile phase.

b. Alkali degradation studies

From 100 \( \mu \text{g/ml} \) of stock solution of Fimasartan pipette out 1 ml To this add 1 ml of 0.1 N NaOH. Finally make up the solution to 10 ml with ACN and keep it for 60 min and check the peak area by injecting the sample into HPLC system using the optimized mobile phase.

c. Oxidative degradation studies

From 100 \( \mu \text{g/ml} \) of stock solution of Fimasartan pipette out 1 ml To this add 1 ml of 3% \( \text{H}_2\text{O}_2 \) finally make up the solution to 10 ml with ACN and keep it for 60 min and check the peak area by injecting the sample into HPLC system using the optimized mobile phase.

d. Photolytic degradation studies

From 100 \( \mu \text{g/ml} \) of stock solution of Fimasartan pipette out 1 ml. Finally make up the solution to 10 ml with ACN. Place the solution in UV cabinet for 60 min. Check the peak area by injecting the sample into HPLC system using the optimized mobile phase.

e. Thermal degradation studies

From 100 \( \mu \text{g/ml} \) of stock solution of Fimasartan pipette out 1 ml. Finally make up the solution to 10 ml with CAN. Place the solution in hot air oven for 60 min at 60°C. Check the peak area by injecting the sample into HPLC system using the optimized mobile phase.

Above values clearly illustrates that maximum degradation occurs in peroxide followed by acid and alkali. No degradation occurs in photolytic and thermal.

**CONCLUSION**

From obtained result, it was concluded that a simple, rapid, sensitive, linear, accurate, rugged, robust, and precise method was developed for the estimation of Fimasartan by HPLC. Various validation parameters such as specificity, linearity, precision, LOD, LOQ, accuracy, solution stability, and forced degradation studies were carried out. The linearity was obtained in the concentration range of 5 \( \mu \text{g/ml} \)-30 \( \mu \text{g/ml} \) with correlation factor \((r^2)\) 0.999. The %RSD for all the parameters was found to within the limits, that is, <2% and % recovery was also found to within the limits, that is, 98-102%. Hence, it was concluded that the projected method can be used for the determination of Fimasartan by stability indicating and reverse phase HPLC method.

**ACKNOWLEDGMENT**

I would like to thank our Principal Dr. K. Abbulu, CMR College of Pharmacy, Hyderabad, for providing all the necessary facilities. I express my deepest gratitude to Metrochem Labs Pvt., Hyderabad, for providing API of Fimasartan to facilitate the work. I take my pleasure to thank all the teaching and non-teaching staff members for their valuable support during my academics and project.

**AUTHORS’ CONTRIBUTIONS**

Conceived and designed the experiments: Uttam Prasad Panigrahy.

Performed the experiment: A. Sruthi and Uttam Prasad Panigrahy.

Analyzed data: Uttam Prasad Panigrahy.

All authors read and approved the final manuscript.

**CONFLICTS OF INTEREST**

The author declared that they have no conflicts of interest.

**AUTHOR’S FUNDING**

The author(s) received no specific funding for this work.
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