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### Original Research Article

## REVIEW ON STABILITY INDICATING METHOD DEVELOPMENT AND VALIDATION OF FIMASARTAN IN BULK AND DOSAGE FORM.

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### ABSTRACT

The present work was developed on stability indicating methods and validated by using reverse phase high performance liquid chromatography using by bulk and pharmaceutical dosage form. The food and drug administration of korea was approved fimasartan in 2010.The method was developed by using Shimadzu LC prominence-I 2030 model with software of chromeleon. In this method C<sub>18</sub> column (150mm x 4.6mm, 5µm particle size) is use with a flow rate of 0.8 ml/min and retention time is 2.4 min. The mobile phase is used cetoneitrile(0.1%):Orthophosphoric acid(80:20v/v) and uv detector is used. The 265 nm wavelength was used for detection. The stress condition of fimasartan is checked by performing a different chemical stability test like a Acid degradation, oxidative degradation, alkali degradation and photolytic degradation. This developed method was validated as per ICH guidelines and found to be precise, accurate and specific. The different peak showing by standard drug and dosage form was compared with each other hence this method is used for to

check quality of this drug. The wide range of accuracy, precision, linearity, retention time, sensitivity and mobile phase suitable to find out impurities in bulk and pharmaceutical dosage form. The LOD was found to be 1.3 µg/ml. The concentration range of linearity is to be 5-30 µg/ml.

**KEYWORDS:** Introduction of Fimasartan, RP-HPLC, Impurity, Stability, C<sub>18</sub> Column.

## INTRODUCTION:-

Fimasartan is anti-hypertensive drug. Fimasartan specially act on rennin angiotensin system of kidney and them breakdown angiotensinogen into angiotensin I. Fimasartan block the AT<sub>1</sub> hence they inhibits the vasoconstriction favoring a vasodilation. The chemical name of this drug is 2-[2-butyl-4-methyl-6-oxo-1-[[4-[2-(2H-tetrazol-5-yl) phenyl] phenyl] methyl] pyrimidin-5-yl]-N and N-dimethylethanethioamide. In Literature survey of fimasartan there is availability of few methods such as High performance liquid chromatography, Lc-MS, Ultra-Violet in bulk and pharmaceutical dosage forms. The present method gives the accurate information regarding method development and validation of fimasartan in bulk and dosage form by using a uv detector at 265 nm. The 265 nm wavelength is accurate, simple, economic, sensitive, reproducible and rapid according to acceptance and prodedure criteria base on ICH guidelines and Food and Drug Administration guidelines.

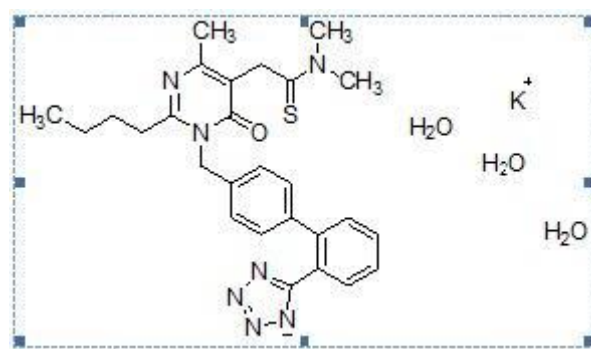


Fig. Structure of Fimasartan

## Drug prone:

Drug	Fimasartan
IUPAC Name	N-[4-(4-methylpiperazin-1-yl)phenyl]-9-(oxan-4-yl)-8-phenylsulfanylpurin-2-amine
Chemical Formula	C <sub>27</sub> H <sub>31</sub> N <sub>7</sub> OS
Mol. Mass	501.6g/mol
Melting Point	267 <sup>0</sup> C to 268 <sup>0</sup> C
Physical State	Solid
Solubility	Fimasartan is freely soluble in methanol and dimethyl sulfoxide. Sparingly soluble in water, slightly soluble in acetone and acetonitrile.
pKa	9.84 to 13.2 hours.
Therapeutic Use	Use in the treatment of hypertension (Anti-Hypertensive)

**Chemical and reagents:**

The drug was procured as gift sample from metrochem pvt.ltd. Hyderabad, Indian. The pharmaceutical dosage form is available by brand name of Fimanta 120 mg manufactured by Ajanta Pharma Limited. The mobile phase chemical was available in HPLC grade acetonitrile, water and orthophosphoric acid were obtained from Merck,Hydrabad, India.

**Selection of wavelength:**

The selection of wavelength by dissolving sample into solvent (acetonitrile) and the resulting solution scanned in UV region inbetween 200-400 nm. The maximum absorption showed at 265 nm.

**Preparation of mobile phase:**

The mobile phase is prepared by dissolving 80 ml of acetonitrile and 20 ml 0.1% orthophosphoric acid in the ratio of 80:20 v/v. 0.1% OPA was prepared by accurately measuring of 0.1 ml of OPA and dissolving in 100 ml of HPLC grade water. The above prepared mobile phase is sonicated and degassed.

**Preparation of standard solution:**

Weighing accurately 100 mg of drug and transferring into 100 ml volumetric flask. Then add few drops of acetonitrile and dissolve the fimasartan properly. Finally make up the volume to 100 ml by using acetonitrile (1000 µg/ml)

**Lituration Survey:**

Sr. No.	Drug Name	Description	Ref. No.
01.	Fimasartan	Column: 1) Hypersil 5 ODS C18 (250×4.6mm, 5µ), 2) Zodiac C18 (250×4.6mm,5µ), 3) Prontosil (250×4.6mm,5µ). Mobile Phase : Methanol 100%:Buffer PH-3 (50:50 v/v) Flow rate : 1.0-1.5 ml/min. Run Time: 50 Min Retention time: 20.325. Detector : UV detector Wavelength: 230 nm LOQ: 4.67ug/ml LOD: 1.54ug/ml	
02.	Fimasartan	Column: C18 Column (250 × 4.6 mm, 5µm particle size) Mobile Phase : Phosphate buffer: Acetonitrile (50:50 v/v) Flow rate : 1ml/min Pump: Shimadzu LC-20AD PUMP(binary) Detector : PDA M20A Diode array detector by using Hypersil BDS Wavelength: 262 nm LOQ: 4.67ug/ml LOD: 1.54ug/ml	

03.	Fimasartan	Column: Phenyl-Hexyl column (Lunaw, 5 mm, 50 mm 3 2.0 mm, Phenomenex) Mobile Phase: mobile phase A (distilled water with 0.1% formic acid) and mobile phase B (100% acetonitrile with 0.1% formic acid) Flow rate: 0.25 ml/ min Precision: <14.9% Accuracy: 91.9% Temperature: 25 <sup>0</sup> C	
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## Results and Discussion:

### Specificity:

The blank solution from formulation with excipients was injected into the system. There is no peaks were detected in the retention time corresponding to analyte peak, this result indicate no interference of excipient of the formulation which indicate that the method develop is having the specificity. The peak of STD and chromatogram is given in fig.

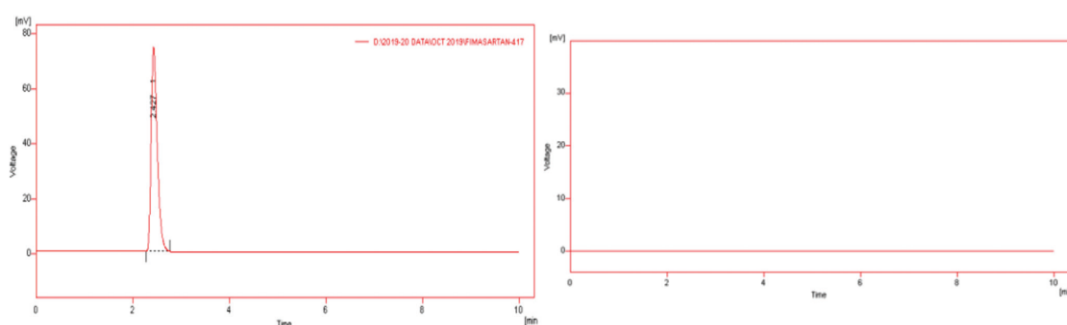


Fig. 3: Blank and standard chromatogram of Fimasartan

### Linearity:

Take a 100 ml volumetric flask and in that add ten milliliters of standard solution and make up volume up to 100 ml using acetonitrile (100 $\mu$ g/ml). Further dilution was made in the concentration range of 5  $\mu$ g/ml-30  $\mu$ g/ml. Then this dilutions injected trice 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 linearity of this method is good ( $r_z = 0.9995$ ). The linearity graph and table were given in the table-2 & Fig.4.

Table 2: Linearity table of Fimasartan	
Concentration ( $\mu$ g/ml)	Peak area (mV)
5	317.684
10	625.400
15	894.706
20	1176.303
25	1476.828

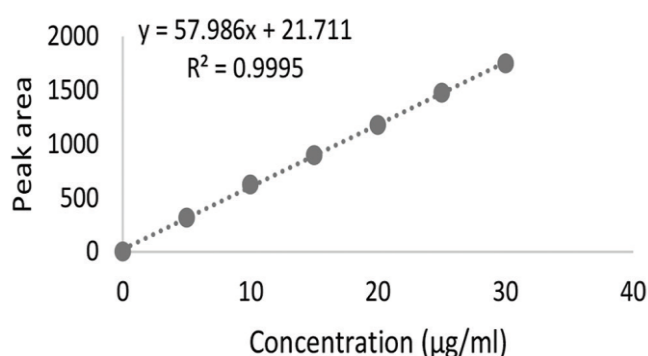


Fig. 4: Linearity curve of Fimasartan

30	1749.634
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**Limit of detection (LOD):**

The low concentration of fimasartan can be detected .This can be calculated by using following formula:

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

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

**Limit of quantification (LOQ):**

The lowest concentration of analyte is find out by using following formula:

$$\text{LOD} = 10 \times \text{Standard deviation/slope}$$

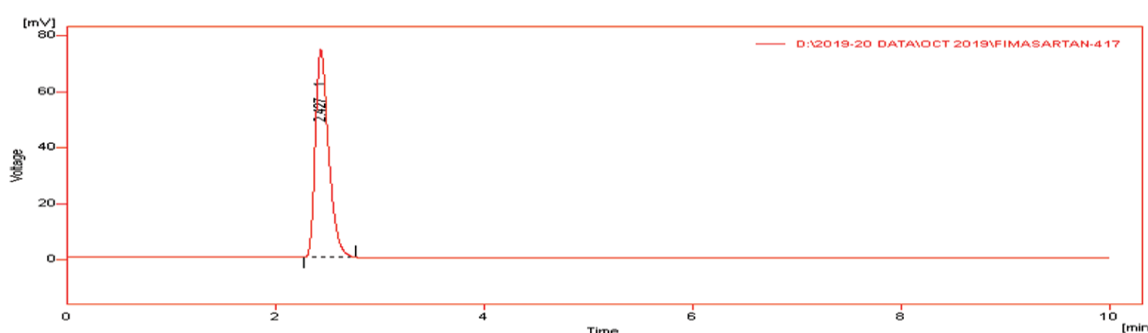
By calculation it was found as 4 µg/ml.

**Precision:****Repeatability****System precision:**

This parameter is perform by injecting 10µg/ml of standard solution of 6 times into High Performance Liquid Chromatography system and record the peak areas and calculate the SD, average and %RSD which shown in Table 4 and Fig.5

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

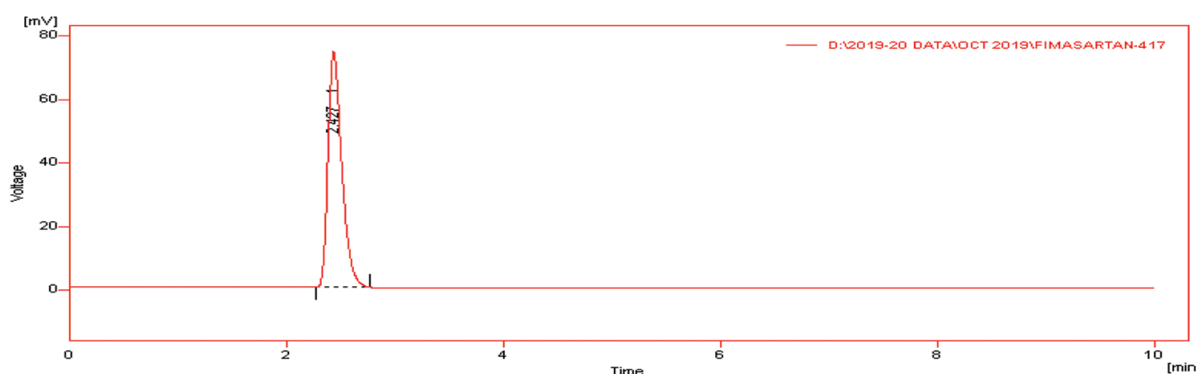
Conc.µg/ml	Retention time	Peak area (mV)	Average peak area (mV)	SD	%RSD
10	2.4	625.410	626.33	1.34	0.21
10	2.4	626.675			
10	2.4	625.054			
10	2.4	628.253			
10	2.4	627.430			
10	2.4	625.138			

**Fig. 5: System precision peak of Fimasartan****Method precision:**

This parameter is performed by injecting 10µg/ml of sample solution six times in the HPLC system and recorded peak areas and calculates the % assay, average, SD, and %RSD which is shown in Table no.5 and Fig.6

**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			

**Fig. 6: Method precision peak of Fimasartan**

Sr. No.	Drug Name	Description	Reference No.
01.	Fimasartan	Column: C18 Column (150 mm× 4.6 mm, 5µm Particle size) Mobile Phase : Acetonitrile (0.1%):Orthophosphoric Acid (80:20 v/v) Flow rate : 0.8ml/min. Detector : UV Detector Wavelength: 265 nm Retention Time: 2.4 min. Linearity: 5-30 µg/ml. LOD: 4 µg/ml.	10

**Procedure for FDS studies:****a. Acid degradation studies:**

Take a 100 µg/ml stock solution of drug and pipette out 1 ml to this add 1 ml 0.1 N HCL finally make up volume upto 10 ml with ACN and kept for 60 min and check out the peak area by injecting sample into high performance liquid chromatography by using the mobile phase.

**b. Alkali degradation studies:**

Take a 100 µg/ml stock solution of drug and pipette out 1 ml to this add 1 ml 0.1 N NaOH. Finally make up volume upto 10 ml with ACN and kept for 60 min and check out the peak area by injecting sample into high performance liquid chromatography by using the mobile phase.

**c. Oxidative degradation studies:**

Take a 100 µg/ml stock solution of drug and pipette out 1 ml to this add 1 ml of 3% H<sub>2</sub>O. Finally make up volume upto 10 ml with ACN and kept for 60 min and check out the peak area by injecting sample into high performance liquid chromatography by using the mobile phase.

**d. Photolytic degradation studies:**

Take a 100 µg/ml stock solution of drug and pipette out 1 ml. Finally make up volume upto 10 ml with ACN. and place the solution in UV cabinet for 60 min and check out the peak area by injecting sample into high performance liquid chromatography by using the mobile phase.

**e. Thermal degradation studies:**

Take a 100 µg/ml stock solution of drug and pipette out 1 ml. Finally make up volume upto 10 ml with ACN. Place the solution in hot air oven for 60 min at 60<sup>0</sup> C and check out the peak area by injecting sample into high performance liquid chromatography by using the mobile phase.

**CONCLUSION:**

Fimasartan is an anti-hypertensive drug. It is approved in 2010 by Food and Drug Administration of Korea. The above analytical methods were developed for estimation of fimasartan by using RP-HPLC instrument. This review illustrated various analytical approaches exercised for evaluation of fimasartan and had performed HPLC, RP-HPLC, UV& stability study in bulk and pharmaceutical dosage form. This method is usefull for detection of quality and quantity of bulk and pharmaceutical dosage form. Analysis of drug is an important role during formulation to identify the drug, its content and metabolites.

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