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# VALIDATION OF THE HPLC METHOD FOR THE ANALYSIS OF METAMITRON IN BULK AND COMERCIAL DOSAGE FORMS

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**ABSTRACT**

A simple, economic, selective, precise, and accurate High Performance liquid Chromatographic method for the analysis of Metamitron in bulk and comercial formulations was developed and validated in the present study. The mobile phase consists of a mixture of Methanol and water in the proportion 70:30 and adjust the pH to 6.0 ± 0.05 with sodium hydroxide solution. This was found to give a sharp peak of Metamitron at a retention time of 4.421min. HPLC analysis of Metamitron was carried out at a wavelength of 310 nm with a flow rate of 1.0 mL/min. The linear regression analysis data for the calibration curve showed a good linear relationship with a regression coefficient of 0.999 in the concentration range of 50 µg $ml^{-1}$ to 150 µg $ml^{-1}$. The linear regression equation was y =2505x-112.6. The developed method was employed with a high degree of precision and degradation for the analysis of Metamitron. The developed method was validated for precision, robustness, detection and quantification limits as per the ICH guidelines. The wide linearity range, sensitivity, short retention time and composition of the mobile phase indicated that this method is better for the quantification of Metamitron.

**Key Words**: Metamitron, HPLC, Validation.

## INTRODUCTION

A survey of the literature revealed that different analytical techniques for the assay of MTM have been reported. Voltametric detection of the herbicide Metamitron at a bismuth film electrode in nondeaerated solution (Arribas AS *et al.,* 2006). Electroanalisis of Metamitron and metribuzen on lignin By Adsorption, (Ludivik J *et al.,* 2000) Electrochemical reduction of Metamitron, (Ludivik J *et al.,* 1998). Identification of different products obtained by electrochemical and photochemical reduction of the Metamitron (Olmedo C *et al.,* 1994). Votametric determination of Metamitron with an elctrogenerated molecularity imprinted polymer microsencer (Gomez-caballero A *et al.,* 2007) Electrochemical determination of the effect of lead (II) on the photochemical degradation of the pesticide Metamitron (Sancho D *et al.,* 1999). Votametric determination of Herbicide Metamitron using Mercury and silver solid amalgam electrode (Selesovska R *et al.,* 2004) Preconcentration and votametric determination of the herbicide Metamitron with a silica modified carbon paste electrode (Arranz A *et al.,* 1997) Determination and method validation of Metamitron in soil by RP-HPLC (Kumar S, *et al.,* 2014). Electrochemical determination of the effect of Copper (II) on the photochemical degradation of the pesticide Metamitron (Sancho D *et al.,* 1999).

Early, analysis of Metamitron in Human plasma by HPLC with fluorescence detection , HPLC determination of Metamitron polyglutamates after Low-Dose Metamitron therapy in patients with Rheumatoid arthritis. Quality control of Metamitron by HPLC and Polarographic and voltammetric methods for the quantitation of MTM in pharmaceuticals and plasma samples have been published.

There is however no reported HPLC method for the analysis of Metamitron in its technical grade and

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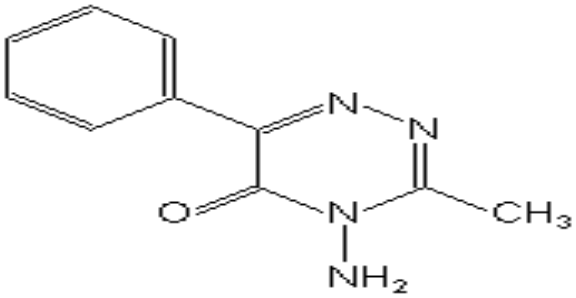
formulations. This is describes a validated HPLC method for the quantitative determination of Metamitron. The empirical formula for Metamitron is $C_{10}H_{10}N_4O$ and the molecular weight is 202.2 grams. It has the following structure.




The HPLC method described here is simple, sensitive, and reproducible for Metamitron determination in Formulations with low background interference. An attempt has been made to develop and validate to ensure there, precision and other analytical method validation parameters as mentioned in various gradients. One method reported for the HPLC determination for developed based on the use of a C-18 column, with a suitable mobile phase, without the use of any internal standard. For formulation the proposed method is suitable for their analysis with virtually no interference of the usual additives presented in formulations.

## MATERIALS AND METHODS

### *Instrumentation*

HPLC Analytical column Chromolith RP-C18, 150 mm x 4.6mm x 10 µ is used for analysis of metamitron

### *Preparation of Mobile phase*

For isocratic system, prepare a mixture of Methanol and water in the proportion 70:30 respectively. Mix well, adjust the pH to 6.0 ± 0.05 with sodium hydroxide pellets. Filter through 0.2 µ Nylon membrane filter paper and degas prior to use.

### *Chromatographic conditions*

Separation was performed on C -18, 100mm x 6mm x 5µ Column. Dimethyle Sulfoxide used as a Diluent and Mobile phase consists of mixture of Methanol and water in the proportion 70:30. Injection volume of 20 µl was used. Mobile phase was filtered before use through 0.5 µm Nylon membrane filter paper and degassed with helium purge for 10 min. The components of the mobile phase were pumped from solvent reservoir to the column at flow rate 1.0 ml $min^{-1}$ and wavelength was set to 310 nm. The column temperature was set at 25$^oC$.

### *Preparation of Metamitron Standard Solution: (Pure sample)*

Weigh accurately about 50 mg of Metamitron working Standard and transfer to a 20 ml volumetric flask. Add 10 ml of diluent and sonicate to dissolve. Dilute to volume with diluent and mix. Transfer 1.0 ml of solution into a 10 ml of volumetric flask and dilute to volume with the diluent and mix. (Dilution scheme: 50mg → 50.0 ml → 1 ml /10.0 ml)

### *Preparation of Test Solution: (Formulation)*

Weigh accurately about 70 mg of sample and transfer to a 50 ml volumetric flask. Add 10 ml of diluent and sonicate to dissolve. Dilute to volume with diluent and mix. Transfer 1.0 ml of solution into a 10 ml of volumetric flask and dilute to volume with the diluent and mix. (Dilution scheme: 70mg → 50.0 ml → 1 ml /10.0 ml)

## RESULTS AND DISCUSSIONS

The appropriate wavelength in UV region has been selected for the measurment of active ingredient in the proposed method. This method was validated by linear fit curve and all the other parameters were calculated.

### *Parameters fixation*

In developing methods, systematic study of the effects of various parameters was undertaken by varying one parameter at a time controlling all other parameters. The following studies were conducted for this purpose.

### *Mobile phase characteristics*

In order to get sharp peaks and baseline separation of the components, carried out number of experiments by varying different components like percentage of organic phase in the mobile phase, total $p^H$ of the selected mobile phase and flow rate by changing one at a time and keeping all other parameters constant. The optimum conditions obtained were included in the procedure proposed.

### *Detection Characteristics*

To test whether Metamitron had been linearly eluted from the column, different amounts of Metamitron were taken and analyzed by the above mentioned procedures. The peak area ratios of component areas were calculated and the values are graphically represented in Fig1.1, the linear fit of the system was illustrated graphically. Least square regression analysis for the method was carried out for the slope, Intercepts and correlation coefficient. The results are presented in Table - 1.

### *Performance Calculations*

To ascertain the system suitability for the proposed method, a number of statistical values have been calculated with the observed readings and the results are recorded in Table-1.

### *Method validations*

The UV absorption maximum for Metamitron was fixed at 310 nm respectively. As the final detection was

made by the UV - absorption spectrum, each method was validated by linear fit curve.

***Precision***

The precision of the method was ascertained separately from the peak area ratios obtained by actual determination of a fixed amount of sample. The percent of Relative Standard deviation calculated for Metamitron and are presented in Tables-7,8,9,10,11&12. The precision of the assays was also determined in terms of intra and inter-day variation in the peak areas for a set of sample solution was calculated in terms of coefficient of variation (CV)

***Interference Studies***

The effect of wide range of excipients and other additives usually present in the formulations of Metamitron in the determinations under optimum conditions were investigated. The common excipients such as colloidal Silicon dioxide, ethyl cellulose, hydroxyl propyl methyl cellulose, magnesium state, microcrystalline cellulose provide have been added to the sample solutions and injected. They have not disturbed the elution or quantification of Drug. In fact many have no absorption at this $\lambda_{max}$

***Analysis of Formulation***

To find out the stability of the proposed methods for the assay of formulations containing Metamitron was analyzed by the proposed and reference methods. The proposed method does not differ significantly in precision from reference method. The results are recorded in Table-3.

***Forced degradation***

There is no interference between the peaks obtained for the chromatograms of degradation preparations. The degradation peaks under forced degradation are well separated from each other. The peak purity for Metamitronpeak is passing.

Hence, the method is very precise, selective and specific to the estimation of Assay of Metamitronin in Metamitron SG 700 g/l by HPLC and the same method is stability indicating, as the degraded products are well separated from Metamitronand as well from each adjacent peaks.

***Ruggedness and Robustness***

Ruggedness of the proposed method was determined by carrying out the analysis by two different analysts using similar operational i.e. Robustness with Change in Column Lot, Change in Flow rate, Change in wavelength and Change in $p^H$ of the Mobile phase . The results were indicated by % CV in Tables – 13,14,15,16,17,18,19,20. Robustness of the method was determined by carrying out the analysis at two different wavelengths i.e. at 308 nm and 312 nm and the results were indicated by % CV in Table -18..

***Solution Stability***

The stability of the solutions under study was established by keeping the solution at room temperature for 48 Hours. The results indicate no significant change in assay values indicating stability of Drug in the solvent used during analysis. The results are recorded in Table -21.

***Robustness***

***Change in Column Lot***

[Normal Experimental Condition: Chromolith RP - C18, 150mm x 4.6mm x 5µ**)**

The system suitability criteria were found to meet the pre-established acceptance criteria as per the analytical method. (Refer to Table - 13 for system suitability results).

***Change in Flow Rate (± 0.2 mL/minute)***

**(Normal Experimental Condition: 1.0ml/minute)**

The system suitability criteria were found to meet the pre-established acceptance criteria as per the analytical method. (Refer to Table - 15 for system suitability results).

***Change in composition of Mobile Phase (± 20ml)***

**(Normal Experimental Condition: methanol:water = 700ml:300ml)**

The system suitability criteria were found to meet the pre-established acceptance criteria as per the analytical method (Refer to Table - 19 for system suitability results)

**Table 1. Performance calculations, detection characteristics precision and accuracy of the proposed method for Metamitron**

| Parameter | HPLC Method |
|---|---|
| Wavelength (nm) | 310 |
| Retention time (t) min | 4.421 |
| Linearity range ( µg $ml^{-1}$) | 50-150 |
| LOD( µg $ml^{-1}$) | 0.1648 |
| LOQ( µg $ml^{-1}$) | 0.5494 |
| Regression equation (y=bc+a) | |
| Slope (b) | 2.506 |
| Intercept (a) | 11.26 |
| Standard deviation (SD) | 0.1377 |

| | |
|---|---|
| Correlation coefficient($r^2$) | 0.9996 |
| Relative Standard deviation (%RSD)* | 0.57563 |
| Intermediate Precision (%RSD) | 0.33 |
| Range of errors | |
| Confidence limits with 0.05 level | 0.120740 |
| Confidence limits with 0.01 level | 1.58680 |

***RSD of five independent determinations**

**Table 2. System suitability - Selectivity**

| Sr. No. | Area of Metamitron |
|---|---|
| 1 | 2012.74 |
| 2 | 2041.60 |
| 3 | 2064.33 |
| 4 | 2084.38 |
| 5 | 2079.97 |
| **Mean** | **2056.60** |
| **Standard Deviation (±)** | **29.69** |
| **(%) Relative Standard Deviation** | **1.44** |

**Table 3. System suitability – Forced Degradation**

| Sr. No. | Area of Rilpivirine HCl |
|---|---|
| 1 | 2372.75 |
| 2 | 2386.89 |
| 3 | 2368.82 |
| 4 | 2387.88 |
| 5 | 2377.95 |
| **Mean** | **2378.86** |
| **Standard Deviation (±)** | **8.44** |
| **(%) Relative Standard Deviation** | **0.35** |

**Table 4. Conditions – Forced Degradation**

| Sample stress condition | Description of stress condition |
|---|---|
| Acid degradation | 5N HCl heated at about 60°C for 10 min on a water bath. |
| Alkali degradation | 5N NaOH heated at about 60°C for 10 min on a water bath. |
| Thermal degradation | 105ºC for 12 hours |
| UV degradation | expose to UV-radiation for 7 days |
| **Acid Stress** | **% Degradation** |
| Standard | 0.159 |
| Sample | 0.045 |
| **Alkali Stress** | **% Degradation** |
| Standard | 0.006 |
| Sample | 0.026 |
| **Thermal Stress** | **% Degradation** |
| Standard | 0.087 |
| Sample | 0.128 |
| **UV Stress** | **% Degradation** |
| Standard | 0.068 |
| Sample | 0.128 |

***Linearity***

**Table 5. System suitability - Linearity of standard**

| Sr. No. | Area of Metamitron |
|---|---|
| 1 | 2315.39 |
| 2 | 2312.67 |
| 3 | 2300.06 |
| 4 | 2317.26 |
| 5 | 2310.30 |
| **Mean** | **2311.14** |
| **Standard Deviation (±)** | **6.73** |
| **(%) Relative Standard Deviation** | **0.29** |

**Table 6. Results of linearity of standard**

| Linearity Level | Sample Concentration (in %) | Sample Concentration (in ppm) | Peak Area | Correlation Coefficient |
|---|---|---|---|---|
| Level – 1 | 50 | 50 | 1147.52 | **0.999** |
| Level – 2 | 75 | 75 | 1786.11 | |
| Level – 3 | 100 | 100 | 2359.04 | |
| Level – 4 | 125 | 125 | 3000.74 | |
| Level – 5 | 150 | 150 | 3672.41 | |

***Precision: System Precision***

**Table 7. System precision**

| Sr. No. | Area of Metamitron |
|---|---|
| 1 | 2148.90 |
| 2 | 2155.00 |
| 3 | 2170.51 |
| 4 | 2195.91 |
| 5 | 2187.57 |
| 6 | 2181.34 |
| 7 | 2179.71 |
| 8 | 2196.70 |
| 9 | 2167.24 |
| 10 | 2180.10 |
| **Mean** | **2176.30** |
| **Standard Deviation (±)** | **15.98** |
| **(%) Relative Standard Deviation** | **0.73** |

***Method Precision***

**Table 8. System suitability: Method precision Analyst 1 HPLC No.: EH/R&D/HPLC-024**

| Sr. No. | Area of Metamitron |
|---|---|
| 1 | 2205.01 |
| 2 | 2228.60 |
| 3 | 2247.85 |
| 4 | 2236.88 |
| 5 | 2246.03 |
| **Mean** | **2232.87** |

| | |
|---|---|
| **Standard Deviation (±)** | **17.38** |
| **(%) Relative Standard Deviation** | **0.78** |

**Table 9. Results of method precision**

| Test Solution | % Assay of Metamitron |
|---|---|
| 1 | 98.81 |
| 2 | 98.96 |
| 3 | 98.70 |
| 4 | 98.85 |
| 5 | 98.91 |
| 6 | 98.82 |
| **Mean** | **98.84** |
| **Standard Deviation (±)** | **0.09** |
| **(%) Relative Standard Deviation** | **0.09** |

***Intermediate Precision***

**Table 10. System suitability - Intermediate precision Analyst – 2**
**HPLC No.: EH/R&D/HPLC-023**

| Sr. No. | Area of Metamitron |
|---|---|
| 1 | 2736.63 |
| 2 | 2731.58 |
| 3 | 2754.58 |
| 4 | 2749.44 |
| 5 | 2741.26 |
| **Mean** | **2742.70** |
| **Standard Deviation (±)** | **9.34** |
| **(%) Relative Standard Deviation** | **0.34** |

**Table 11. Results of Intermediate precision**

| Test Solution | % Assay of Metamitron |
|---|---|
| 1 | 98.90 |
| 2 | 98.11 |
| 3 | 98.97 |
| 4 | 98.63 |
| 5 | 98.45 |
| 6 | 98.82 |
| **Mean** | **98.65** |
| **Standard Deviation (±)** | **0.32** |
| **(%) Relative Standard Deviation** | **0.33** |

**Table 12. Results of twelve test solutions of Metamitron in Metamitron SC 700 g/l (six of method precision & six of intermediate precision)**

| Analysis performed during method precision study By Analyst 1 on system 1 and on column 1 on day 1 | |
|---|---|
| **Same column** | **% Assay of Metamitron** |
| 1 | 98.81 |
| 2 | 98.96 |
| 3 | 98.70 |

| | |
|---|---|
| 4 | 98.85 |
| 5 | 98.91 |
| 6 | 98.82 |
| **Analysis performed during intermediate precision study** | |
| **Column sr. no.** | **015337030136 01** |
| **Test Solution** | **% Assay of Metamitron** |
| 7 | 98.90 |
| 8 | 98.11 |
| 9 | 98.97 |
| 10 | 98.63 |
| 11 | 98.45 |
| 12 | 98.82 |
| **Mean of twelve samples** | **98.74** |
| **Standard Deviation (±)** | **0.25** |
| **(%) Relative Standard Deviation** | **0.25** |

**Table 13. System suitability - Robustness with Change in Column Lot**

| **Sr. No.** | **Area of Metamitron** | |
|---|---|---|
| | **Same column** | **Diff column** |
| 1 | 2240.97 | 2243.17 |
| 2 | 2245.55 | 2241.79 |
| **Mean** | **2243.26** | **2242.48** |
| **Standard Deviation (±)** | **3.24** | **0.98** |
| **(%) Relative Standard Deviation** | **0.14** | **0.04** |

**Table 14. Results for Change in Column Lot**

| **Flow rate →** | **Same column** | **Diff column** |
|---|---|---|
| **Sample** | **% Assay** | |
| Test solution | 98.81 | 98.12 |
| Average assay result from method precision | 98.96 | 98.84 |
| **Mean** | **98.89** | **98.48** |
| **Standard Deviation (±)** | **0.11** | **0.51** |
| **(%) Relative Standard Deviation** | **0.11** | **0.52** |

**Table 15. System suitability - Robustness with change in flow rate**

| **Sr. No.** | **Area of Metamitron** | |
|---|---|---|
| | **0.8mL/minute** | **1.2 mL/minute** |
| 1 | 2662.11 | 2632.69 |
| 2 | 2643.40 | 2629.28 |
| **Mean** | **2652.76** | **2630.99** |
| **Standard Deviation (±)** | **13.23** | **2.41** |
| **(%) Relative Standard Deviation** | **0.50** | **0.09** |

**Table 16. Results for change in flow rate**

| **Flow rate →** | **0.8mL/minute** | **1.2 mL/minute** |
|---|---|---|
| **Sample** | **% Assay** | |

| | | |
|---|---|---|
| Test solution | 98.83 | 98.25 |
| Average assay result from method precision | 98.84 | 98.84 |
| **Mean** | **98.84** | **98.55** |
| **Standard Deviation (±)** | **0.01** | **0.42** |
| **(%) Relative Standard Deviation** | **0.01** | **0.42** |

***Change in Wavelength (± 2 nm)***

**Table 17. System suitability - Robustness with change in wavelength**

| **Sr. No.** | **Area of Metamitron** | |
|---|---|---|
| | **308nm** | **312nm** |
| 1 | 2231.46 | 2248.85 |
| 2 | 2233.48 | 2246.39 |
| **Mean** | **2644.05** | **2676.45** |
| **Standard Deviation (±)** | **1.43** | **1.74** |
| **(%) Relative Standard Deviation** | **0.05** | **0.06** |

**Table 18. Results for change in wavelength**

| **Wavelength →** | **308nm** | **312nm** |
|---|---|---|
| **Sample** | **% Assay** | |
| Test solution | 98.04 | 98.16 |
| Average assay result from method precision | 98.84 | 98.84 |
| **Mean** | **98.44** | **98.50** |
| **Standard Deviation (±)** | **0.57** | **0.48** |
| **(%) Relative Standard Deviation** | **0.57** | **0.49** |

**Table 19. System suitability - Robustness with change in composition of mobile phase**

| **Sr. No.** | **Area of Metamitron** | |
|---|---|---|
| | **720ml:280ml** | **680ml:320ml** |
| 1 | 2237.07 | 2250.72 |
| 2 | 2260.43 | 2227.42 |
| **Mean** | **2248.75** | **2239.07** |
| **Standard Deviation (±)** | **16.52** | **16.48** |
| **(%) Relative Standard Deviation** | **0.73** | **0.74** |

**Table 20. Results for change in composition of mobile phase**

| **Composition of methanol & water** | **720:280** | **680:320** |
|---|---|---|
| **Sample** | **% Assay** | |
| Test solution | 98.29 | 98.89 |
| Average assay result from method precision | 98.84 | 98.84 |
| **Mean** | **98.57** | **98.87** |
| **Standard Deviation (±)** | **0.39** | **0.04** |
| **(%) Relative Standard Deviation** | **0.39** | **0.04** |

**Table 21. The assay results obtained during solution stability**

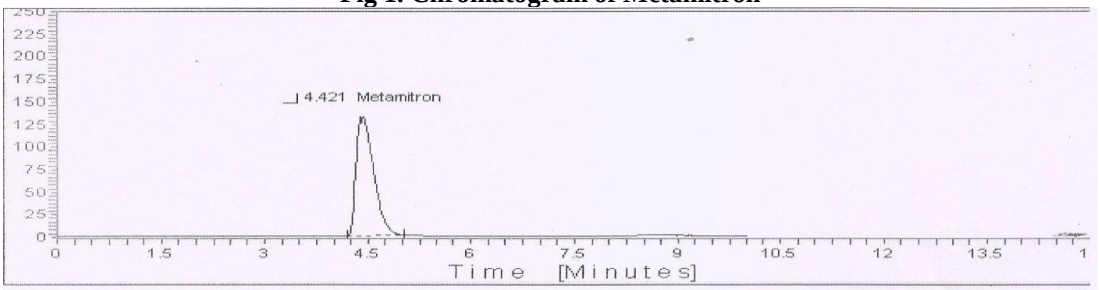
| **TIME** | **Std Area** | **Avg std area** | **Spl area** | **Avg Spl area** |
|---|---|---|---|---|
| $0^{th}$ hr | 2254.63 | 2258.87 | 2292.77 | 2293.185 |
| | 2263.11 | | 2293.6 | |

| | | | | |
|---|---|---|---|---|
| 12th hr | 2247.81 | 2267.825 | 2227.6 | 2231.55 |
| | 2287.84 | | 2235.5 | |
| 24 hr | 2267.64 | 2270.89 | 2207.57 | 2219.92 |
| | 2274.14 | | 2232.27 | |
| 36 hr | 2232.82 | 2251.05 | 2258.69 | 2264.98 |
| | 2269.28 | | 2271.27 | |
| 48 hr | 2277.81 | 2281.155 | 2268.9 | 2258.225 |
| | 2284.5 | | 2247.55 | |
| **Mean** | **2265.96** | **2265.96** | **2253.57** | **2253.57** |
| **Standard Deviation (±)** | **17.02** | **11.52** | **28.52** | **28.89** |
| **(%) Relative Standard Deviation** | **0.75** | **0.51** | **1.27** | **1.28** |

**Table 22. Results for solution stability**

| **% Assay results calculated against the freshly prepared system suitability standard** | |
|---|---|
| **Sample** | **% Assay of Metamitron** |
| 0th hr | 98.98 |
| 12th hr | 98.08 |
| 24 hr | 97.98 |
| 36 hr | 98.77 |
| 48 hr | 98.12 |
| **Mean** | 98.39 |
| **Standard Deviation (±)** | 0.46 |
| **(%) Relative Standard Deviation** | 0.46 |

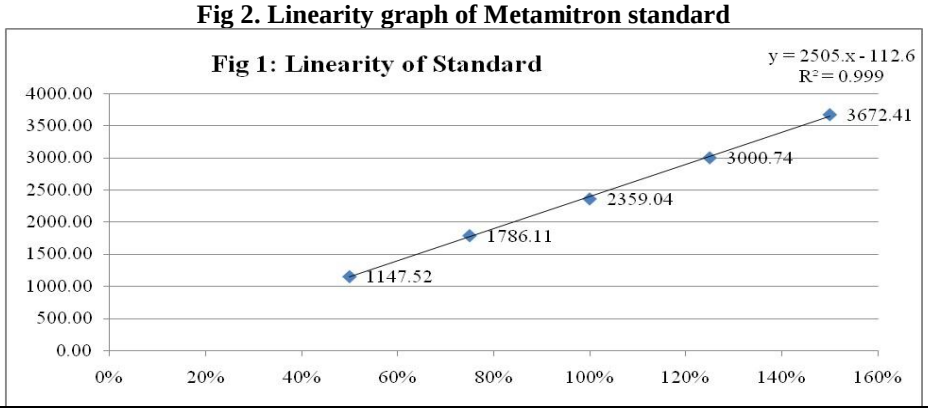
**Fig 1. Chromatogram of Metamitron**




Result-A Table

| Peak No | Retn.Time | Area | Height | Area % | Height % |
|---|---|---|---|---|---|
| 1 | 4.422 | 2359.043 | 131.35 | 100 | 100 |
| Total | | 2359.043 | 131.35 | 100 | 100 |

**Fig 2. Linearity graph of Metamitron standard**



## CONCLUSION

The method was found to be accurate and precise, as indicated by recovery studies close to 100 and % RSD is not more than 2. The summery of validation parameters of proposed HPLC method is given.

The simple, accurate and precise HPLC method for the determination of Metamitron as bulk and form has been developed. The method may be recommended for routine and quality control analysis of the investigated drug in bulk and formulations. The analytical solution is found to be stable up to 48 Hrs at room temperature. Hence, it is concluded that the analytical method is validated and can be used for routine analysis and for stability study.

**ACKNOWLEDGEMENT**: None

**CONFLICT OF INTEREST**:

The authors declare that they have no conflict of interest.

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