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# A New Analytical Method Development and Validation for Related Substances of Rabeprazole in Active Pharma Ingredient by HPLC-PDA Detector

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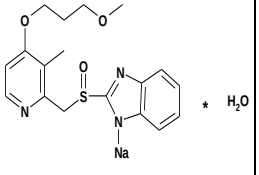
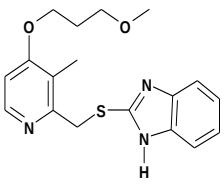
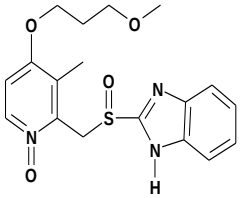
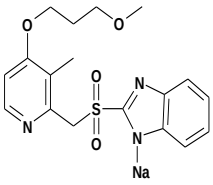
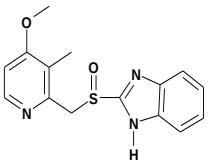
**Abstract :** A simple and inexpensive method was developed with high performance liquid chromatography with PDA detection for determination of Rabeprazole and related impurities (2-[4-(3-Methoxy-propoxy)-3-methyl-pyridin-2-ylmethylsulfanyl]-1H-benzoimidazole, 2-[4 (3-Methoxy-propoxy)-3-methyl-1-oxy-pyridin-2-ylmethanesulfinyl]-1H-benzoimidazole ,2-[4-(3-Methoxy-propoxy)-3-methyl-pyridin-2-ylmethanesulfonyl]-1H-benzoimidazole sodium salt and2-(4-Methoxy-3-methyl-pyridin-2-ylmethanesulfinyl)-1H-benzoimidazole).The chromatographic separations were achieved on (250×4.6 mm), 5.0 µm, Phenomenex C18 column employing 0.02M K2HPO4: Acetonitrile: Methanol (85:5:10 v/v)as mobile phase with gradient programmed at flow rate 1.0 mL/min was chosen. Four impurities were eluted within 30 minutes. The column temperature was maintained at 30°C and a detector wavelength of 285 nm was employed. The method was successfully validated by establishing System Suitability, Specificity, Linearity, Accuracy, limit of detection and Limit of quantification.
**Key words :** HPLC-PDA, Method validation, related impurities, Rabeprazole, LOQ, LOD

## Introduction

Rabeprazole sodium is 2-([4-(3-methoxypropoxy)-3- methyl-2-pyridinyl]-methyl]sulfinyl]-1H benzimidazole sodium salt is an anti-ulcer drug in the class of proton pump inhibitors that reduce the production of acid by blocking the enzyme (hydrogen-potassium adenosine triphosphatase) in parietal cells and used to treat duodenal ulcers and erosive or ulcerative gastro esophageal reflux disease [1, 2]. It is a proton pump inhibitor that covalently binds and inactivates the gastric parietal cell proton pump(H+, K+-ATPase) and is used in the management of acid-related disorders [3, 4 5]. It has also demonstrated efficacy in healing and symptom relief of gastric and duodenal ulcers, as well as a high-eradication rate of the microorganism Helicobacter pylori when associated with antimicrobial therapy [6, 7,8]. Primary use of rabeprazole Sodium is to treat heartburn and gastroesophageal reflux disease, ulcers, bacterial Infection due to Helicobacter pylori and Zollinger-Ellison Syndrome caused by stomach acid[9, 10, 11].

| Compound | IUPAC Name | Structure | Molecular Formula | Molecular Weight |
|---|---|---|---|---|
| Rabeprazole | 2-([4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1H benzimidazole sodium salt Monohydrate |  | $C_{18}H_{20}N_3NaO_3S$ $H_2O$ | 399.43 |

| | | | | |
|---|---|---|---|---|
| Impurity 1 | 2-[4-(3-Methoxy-propoxy)-3-methyl-pyridin-2-ylmethylsulfanyl]-1H-benzoimidazole |  | $C_{18}H_{21}N_3O_2S$ | 343.45 |
| Impurity 2 | 2-[4-(3-Methoxy-propoxy)-3-methyl-1-oxy-pyridin-2-ylmethanesulfinyl]-1H-benzoimidazole |  | $C_{18}H_{21}N_3O_4S$ | 375.44 |
| Impurity 3 | 2-[4-(3-Methoxy-propoxy)-3-methyl-pyridin-2-ylmethanesulfonyl]-1H-benzoimidazole sodium salt |  | $C_{18}H_{20}N_3NaO_4S$ | 397.43 |
| Impurity 4 | 2-(4-Methoxy-3-methyl-pyridin-2-ylmethanesulfinyl)-1H-benzoimidazole |  | $C_{15}H_{15}N_3O_2S$ | 301.37 |

## Materials and Methods

### Materials

Standard gift samples of Rabeprazole and impurities were provided by Dr Benarji Patrudu, Associate Professor, Gitam University, Hyderabad. All the chemicals and reagents used were of analytical grade.

### HPLC Chromatographic Parameters

Chromatographic separation was performed on The HPLC-UV system used, consisted shimadzu high performance liquid chromatography with LC- 20AT pump and SPD-20A interfaced with LC solution software, equipped with a reversed phase C18 analytical column of 250 mm x 4.6 mm and particle size 5 µm (Pheonomenex C18) Column oven temperature was maintained at 35°C and sample temperature was maintained at 5°C.

An HPLC method was developed for Rabeprazole and related impurities by using photo diode array detector. Rabeprazole and all related impurities were injected into HPLC system by changing the different composition of 0.02M $K_2HPO_4$: Acetonitrile: Methanol (85:5:10 v/v). Finally the Rabeprazole and related impurities are separated in the composition as given below.

**Pump A: 0.02M $K_2HPO_4$ , Pump B: Acetonitrile and Pump C: Methanol**

| Time | % of A | % of B | % of C | Flow rate (mL) |
|---|---|---|---|---|
| 0 | 85 | 5 | 10 | 1.00 |
| 10 | 60 | 30 | 10 | 1.00 |
| 15 | 30 | 60 | 10 | 1.00 |
| 25 | 30 | 60 | 10 | 1.00 |
| 35 | 85 | 5 | 10 | 1.00 |
| 40 | 85 | 5 | 10 | 1.00 |

The absorption maxima for Rabeprazole, Impurity –1, Impurity-2, Impurity –3 and Impurity-4 were found to be at 285 nm. The compound was scanned form 200 – 400 nm. Column temperature was set up at 30°C and injection volume as set to 20µL. By follow this analytical method conditions, Rabeprazole and related impurities were separated. Hence, it was concluded that HPLC method was suitable for method validation.

**Method Validation**

**Preparation of dissolution phase**

500 mL of 0.02M $K_2HPO_4$ nd 500 mL of methanol was taken in a 1 liter mobile, shaken vigorously.

**System Suitability**

**Preparation of test solution**

Accurately weighed about 100.0 mg of the substance to be examined and dissolve in 50 ml of dissolution phase.

**Preparation of Reference Solution (a)**

In a 100 ml volumetric flask dissolve about 20 mg of reference standard accurately weighed with dissolution phase and dilute to volume.

In a 100 ml volumetric flask transfer 1 ml of this solution, dissolve and dilute to volume with dissolution phase (0.1% with respect to test solution).

**Preparation of Reference Solution (b) for System Suitability**

Dissolve 20 mg of Impurity 3 in a 100 ml volumetric flask and dilute to volume with dissolution phase. Take 1 ml of the latter solution and dilute (with dissolution phase) in a 100 ml flask containing 100 mg of Rabeprazole Sodium Salt Monohydrate .

**System suitability test**

Resolution – The resolution between the peaks of Rabeprazole Sodium Salt Monohydrate and Impurity 3 not be less than 1.5 in the chromatogram obtained with reference solution (b).

**Procedure**

Program the method. Inject the reference solution b and check the resolution between the peak of Rabeprazole Sodium Salt Monohydrate and Impurity 3. Inject six times 20µl of reference solution (a) and record the chromatograms. Inject the test solution once. Calculate reference standard mean area of Rabeprazole Sodium Salt Monohydrate with all six injections.

The test is invalid if RSD of reference standard areas is more than 3 %.

**Specificity and Selectivity**

The specificity will be confirmed comparing the chromatogram of the blank run to the chromatogram of the single impurity run. Then a solution containing a mixture of impurities and Rabeprazole Sodium Salt Monohydrate will be injected.

The Rabeprazole Sodium Salt Monohydrate peak has to be separated and has to meet the suitability parameters.

In a separate 100 mL volumetric flasks, dissolve 20 mg of the Rabeprazole reference standard, impurity-1, impurity-2, impurity-3 and impurity-4, dissolved an diluted up to the mark with dissolution phase (each solution conc. - 200 µg/ml) and labelled as standard solution-A . 1.0 mL of each solution was transferred into separate 100 ml volumetric flask transfer, dissolve and dilute to volume with dissolution phase (each

solution conc. - 2 µg/ml) and the resulting solutions will be injected in HPLC system and peak purity was determined for adaplane and related impurities.

In a 100 ml volumetric flask pipette 1 ml of the standard solution -A of each impurity and of Rabeprazole, previously prepared, dissolve and dilute to volume with dissolution phase. Inject the obtained solution 6 times for its selectivity.

**Linearity**

About 20 mg of the Rabeprazole reference standard, 20 mg of impurity-1, 20 mg of impurity-2, 20 mg of impurity-3 and 20 mg of impurity-4 was weighed in a 100 mL volumetric flasks, dissolved an diluted up to the mark with dissolution phase and labelled as Stock Solution. From stock solution of Rabeprazole and impurities having concentrations of 200 µg/mL was taken for linearity test. 0.2, 0.5, 1.0, 1.5 and 2.0 mL of standard stock solution of Rabeprazole and impurities was transferred into separate 100 mL volumetric flask and diluted up to the mark with dissolution phase to get the final concentration of 0.4, 1.0, 2.0, 3.0 and 4.0 µg/mL respectively. The linearity was in the range of 20 – 200 % for A.I and impurities. The resulting solutions were injected into HPLC in three replications at 285 nm. Correlation coefficient was calculated for A.I and impurities by plotting the graph between concentrations versus peak Area.

**Precision**

The Precision will be determined in agreement with ICH guidelines, injecting six different solutions containing both impurities and Rabeprazole at the test concentration (six solutions with different weights are prepared and injected). In a separate 100 mL volumetric flasks, dissolve 20 mg of the Rabeprazole, impurity-1, impurity-2, impurity-3 and impurity-4 and dissolve with dissolution phase (each conc. - 200 µg/ml) and labelled as Solution A. 1.0 mL of solution A was transferred into separate 100 ml volumetric flask transfer, dissolve and dilute to volume with dissolution phase (each impurity conc. - 2 µg/ml).

**Intermediate Precision**

Intermediate precision will be assessed by six injections of test solutions prepared on different days, using fresh mobile phase, as in Precision.

**Accuracy**

The Accuracy will be determined as prescribed by ICH guidelines[12]. Known quantities of impurities are going to be added to Rabeprazole at 50 –100 –150% of the nominal limit of 0.10 % for each impurity . The results obtained have to meet the proposed limits. The scheme to carry out will be applied to every impurity. The experiment is performed in triplicate at each level.

**Test solutions**

Prepare a solution containing all the impurities at a concentration of 200 µg/ml each (20 mg/100 ml; solution A from the linearity test can be used). Transfer respectively 0.5 ml, 1 ml and 1.5 ml of this solution to three different 100 ml volumetric flasks, containing 200 mg of Rabeprazole Sodium Salt Monohydrate each one and diluted to volume with dissolution phase.

**LOD and LOQ**

LOD and LOQ will be assessed in accordance with ICH guidelines (13). The method chosen is based on Signal-to-noise ratio, using the following formulas:

$$LOD = \frac{3 \times s}{S} \qquad LOQ = \frac{10 \times s}{S}$$

## Results and Discussions

### System suitability

The resolution between the peaks of Rabeprazole and Impurity 3 are more than 1.5 and % RSD of reference standard areas is not less than 3 % on each day of analysis. Hence the system suitability passes the acceptance criteria.

The suitability of method was confirmed by verifying the USP's parameters like retention times (RT), theoretical plates (N), tailing factors (T), Relative Standard Deviation and resolution (R).

| | | |
|---|---|---|
| Resolution (R) = $2*\frac{(t_2-t_1)}{(W_1+W_2)}$ | Tailing factor (T) = $\frac{W_{5\%}}{2f}$ | Theoretical plates (N)= $5.54*\left(\frac{t}{W_{h/2}}\right)^2$ |

W: width of peak at the baseline, measured by extrapolating the relative straight sides to the baseline

W5%: width of peak at 5% of height

Wh/2: width of peak at half height

f: distance from the peak maximum to the leading edge of the peak. The distance is measured at 5% of height.

### Specificity and Selectivity

The specificity of the method was determined by injecting the individual solutions of A.I (2 µg/mL) and impurities (2 µg/mL) and peak purity was checked. The peak purity was more than 99 % for Rabeprazole and impurities confirm the specificity of the method.

### Linearity

The linearity regression curve for Rabeprazole and their impurities were drawn between concentrations and peak areas. The correlation coefficient is above 0.99 at wavelength of 254 nm for Rabeprazole and their impurities. The results are mentioned in **Table 1.** A calibration curve was showed in F**igure. 1** and Representative chromatograms were presented in F**igure 2 and Figure 3**.

**Table 1: Linearity Data of Rabeprazole and its impurities**

| **Range** | **Concentration in µg/mL** | **Area in mAU-sec of Rabeprazole** | **Area in mAU-sec Impurity-1** | **Area in mAU-sec Impurity-2** | **Area in mAU-sec Impurity-3** | **Area in mAU-sec Impurity-4** |
|---|---|---|---|---|---|---|
| 20% | 0.4 | 14817 | 18247 | 21784 | 16084 | 18089 |
| 50% | 1 | 40471 | 47435 | 57498 | 46518 | 49815 |
| 100% | 2 | 83291 | 96244 | 112741 | 92987 | 99745 |
| 150% | 3 | 124010 | 145155 | 175711 | 131784 | 149689 |
| 200% | 4 | 160184 | 188747 | 224894 | 180771 | 195005 |
| **Slope** | | 40616.55 | 47649.22 | 56957.83 | 44983.83 | 49244.16 |
| **Intercept** | | 72.17 | 55.22 | 53.32 | 62.44 | 40.76 |
| **Correl** | | 0.9994 | 0.9997 | 0.9994 | 0.9993 | 0.9997 |

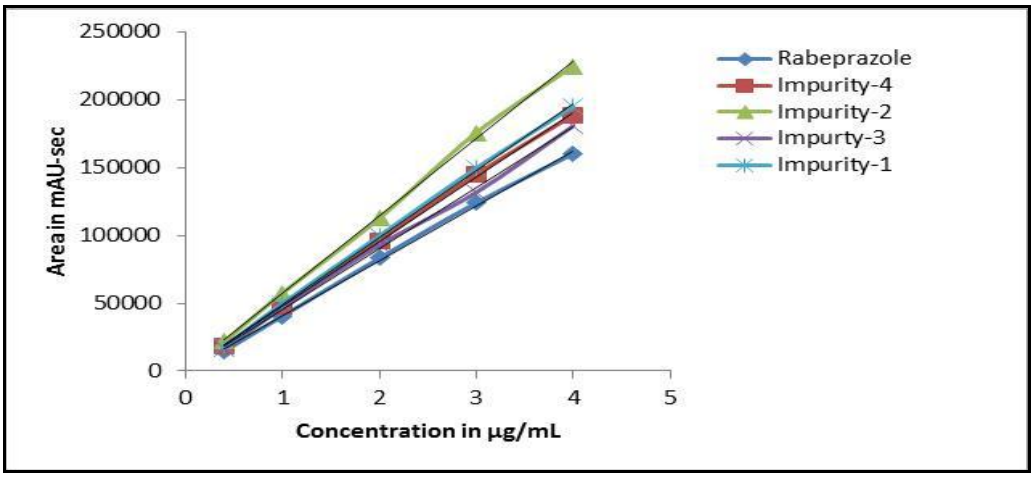



**Figure 1: Calibration curve of Rabeprazole and its impurities**

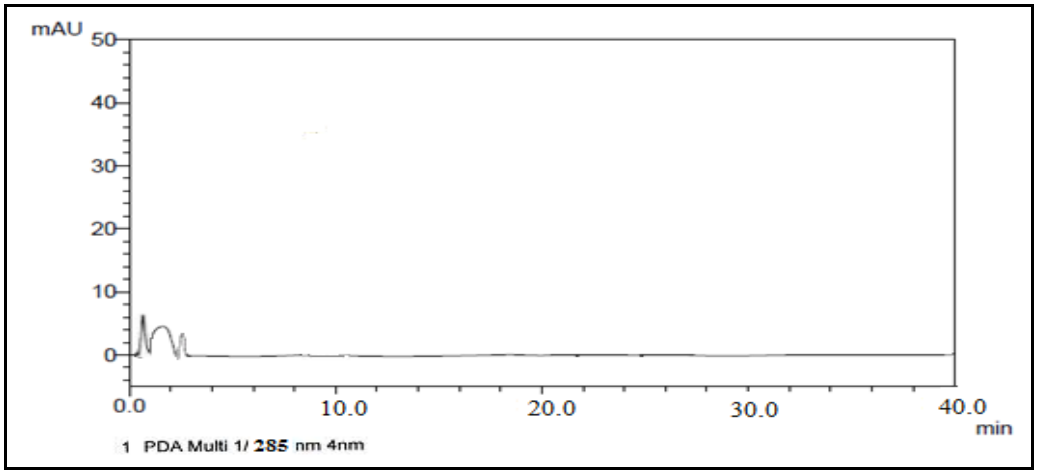



**Figure 2: Representative chromatogram of diluent as mobile phase**

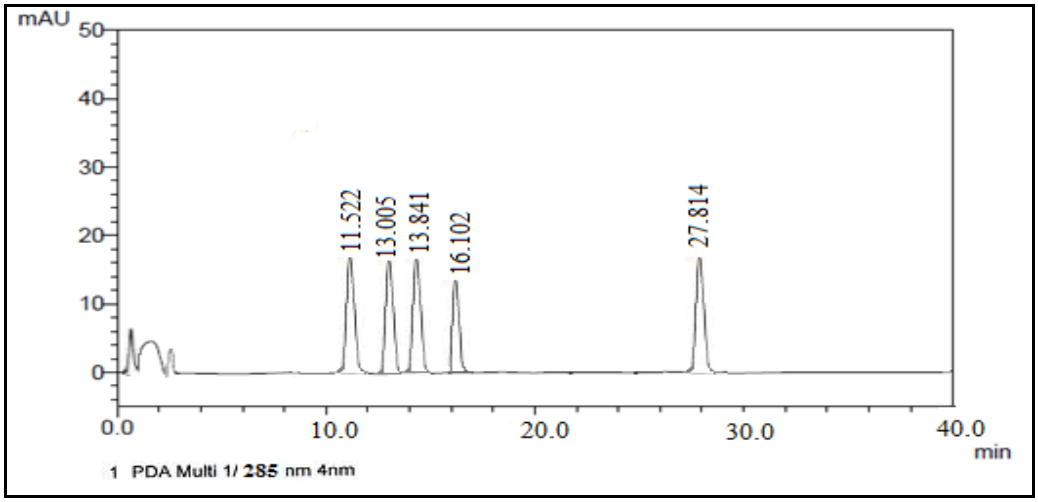



**Figure 3: Representative chromatogram of linearity 2.0 µg/mL**

**Method precision**

Intermediate precision will be assessed by six injections of test solutions prepared on different days, using fresh mobile phase and a different operator as in Precision. The results are mentioned in **Table 2 to Table 6.**

**Table 2: Method Precision of Impurity-1**

| Injection | Weight in mg | Area in mAU.Sec | Day |
|---|---|---|---|
| 1 | 20.25 | 101637 | Day 1 |
| 2 | 20.28 | 102541 | |
| 3 | 20.36 | 103689 | |
| 4 | 20.91 | 104331 | |
| 5 | 20.17 | 98810 | |
| 6 | 20.15 | 99505 | |
| 7 | 20.23 | 106856 | Day 2 |
| 8 | 20.07 | 97955 | |
| 9 | 20.09 | 98639 | |
| 10 | 20.11 | 100839 | |
| 11 | 20.12 | 99761 | |
| 12 | 20.02 | 97335 | |

| **Average** | **100991** |
|---|---|
| STDV | 2896.12 |
| RSD | 2.87 |

**Table 3: Method Precision of Impurity-2**

| Injection | Weight in mg | Area in mAU.Sec | Day |
|---|---|---|---|
| 1 | 20.10 | 114784 | Day 1 |
| 2 | 20.17 | 114897 | |
| 3 | 20.15 | 116956 | |
| 4 | 20.06 | 112145 | |
| 5 | 20.14 | 111895 | |
| 6 | 20.11 | 111524 | |
| 7 | 20.19 | 114996 | Day 2 |
| 8 | 20.21 | 120145 | |
| 9 | 20.25 | 121530 | |
| 10 | 20.17 | 119545 | |
| 11 | 20.16 | 118491 | |
| 12 | 20.13 | 113695 | |

| **Average** | **115883.58** |
|---|---|
| STDV | 3411.85 |
| RSD | 2.94 |

**Table 4: Method Precision of Impurity-3**

| Injection | Weight in mg | Area in mAU.Sec | Day |
|---|---|---|---|
| 1 | 20.16 | 96215 | Day 1 |
| 2 | 20.31 | 97854 | |
| 3 | 20.12 | 96025 | |
| 4 | 20.18 | 96369 | |
| 5 | 20.23 | 96458 | |
| 6 | 20.41 | 98125 | |
| 7 | 20.36 | 97858 | Day 2 |
| 8 | 20.26 | 96982 | |
| 9 | 20.25 | 96912 | |
| 10 | 20.09 | 95874 | |
| 11 | 2011 | 95962 | |
| 12 | 20.18 | 96411 | |

| **Average** | **96753.75** |
|---|---|
| STDV | 795.59 |
| RSD | 0.82 |

**Table 5: Method Precision of Impurity-4**

| Injection | Weight in mg | Area in mAU.Sec | Day |
|---|---|---|---|
| 1 | 20.14 | 95214 | Day 1 |
| 2 | 20.21 | 95745 | |
| 3 | 20.26 | 95874 | |
| 4 | 20.29 | 96325 | |
| 5 | 20.33 | 96851 | |
| 6 | 20.39 | 97012 | |
| 7 | 20.15 | 95366 | Day 2 |
| 8 | 20.06 | 94568 | |
| 9 | 20.03 | 94697 | |
| 10 | 20.18 | 95968 | |
| 11 | 20.14 | 95740 | |
| 12 | 20.25 | 95813 | |

| | |
|---|---|
| **Average** | **95764.42** |
| STDV | 747.16 |
| RSD | 0.78 |

**Table. 6. Method Precision of Rabeprazole**

| Injection | Weight in mg | Area in mAU.Sec | Day |
|---|---|---|---|
| 1 | 20.36 | 88254 | Day 1 |
| 2 | 20.41 | 89235 | |
| 3 | 20.39 | 88564 | |
| 4 | 20.29 | 87145 | |
| 5 | 20.22 | 87005 | |
| 6 | 20.26 | 87129 | |
| 7 | 20.24 | 87187 | Day 2 |
| 8 | 20.15 | 86874 | |
| 9 | 20.11 | 85987 | |
| 10 | 20.04 | 85006 | |
| 11 | 20.09 | 85236 | |
| 12 | 20.17 | 86459 | |

| | |
|---|---|
| **Average** | **87006.75** |
| STDV | 1261.62 |
| RSD | 1.45 |

**Accuracy**

**Preparation of Test solutions**

Prepare a solution containing all the impurities at a concentration of 200 µg/ml each (20 mg/100 ml; solution from the linearity test can be used). Transfer respectively 0.5 ml, 1 ml and 1.5 ml of this solution to three different 200 ml volumetric flasks, containing 300 mg of Rabeprazole each one.

The dilutions have to be carried out for each solution of the linearity test (total: 3x3 test solutions). The representative chromatogram showed in **Figure 4** and results were presented in **-**

**Table 7: Recovery results of Rabeprazole impurities.**

| % | Impurity -1 | Impurity -2 | Impurity -3 | Impurity -4 |
|---|---|---|---|---|
| 50 | 91.21 | 93.28 | 90.25 | 94.23 |
| 50 | 91.58 | 93.45 | 91.23 | 95.26 |
| 50 | 92.29 | 94.12 | 93.65 | 95.21 |
| 100 | 93.14 | 94.58 | 93.47 | 96.06 |
| 100 | 93.98 | 94.95 | 94.12 | 96.32 |
| 100 | 94.21 | 95.06 | 94.39 | 96.41 |
| 150 | 94.87 | 96.87 | 95.63 | 98.21 |
| 150 | 95.29 | 97.05 | 95.89 | 98.56 |
| 150 | 95.17 | 96.87 | 96.06 | 98.74 |

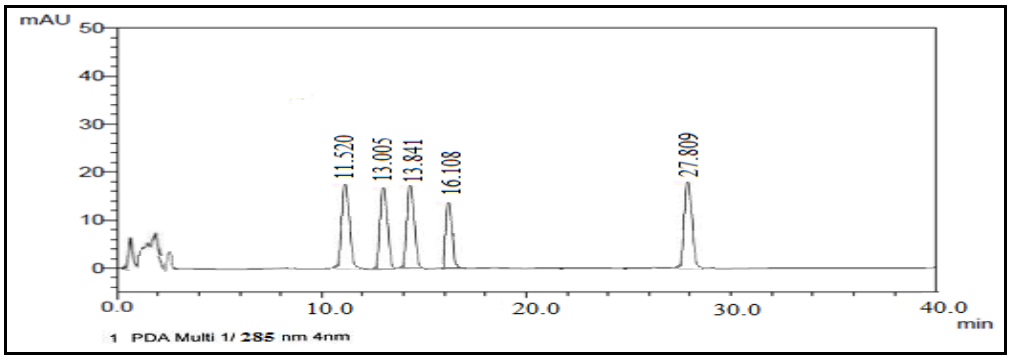



**Figure 4: Representative chromatogram of 100 % fortification level of impurities**

***LOD and LOQ***

The LOD and LOQ are established successfully for each impurity in rabeprazole based on Signal-to-noise ratio method. The results were presented in **Table 8.**

**Table 8: Limit of quantification and Limit of detection results of rabeprazole impurities**

| Impurity | Detection limit (LOD) In µg/mL | Quantitation limit (LOQ) In µg/mL |
|---|---|---|
| **Imp. 1** | 0.02 | 0.06 |
| **Imp. 2** | 0.01 | 0.03 |
| **Imp. 3** | 0.015 | 0.05 |
| **Imp. 4** | 0.02 | 0.06 |

**Calculations**

The Rabeprazole impurities are determined by comparison of peaks areas with the following formula:

$$\text{Percentage Rabeprazole impurity} = \frac{At \times C \times D \times PS}{Ar \times W\ sample \times Fc} \times 100$$

Where:

At: peak area of Impurity obtained by test solution

Ar: peak area of Rabeprazole obtained by reference solution (a)
C: Rabeprazole concentration in reference solution (a) (mg/ml)
D: sample dilution (ml)
W sample: sample weight in test solution (mg)
PS: Purity of reference standard
Fc: Response Factor of Impurity

$$\% \text{ Recovery} = \frac{\text{Recovered Concentration}}{\text{Fortified Concentration}} \times 100$$

## Conclusions

The method developed for quantitative determination of Rabeprazole and its impurities is rapid, precise, accurate and selective. The method was completely validated showing satisfactory data for all method - validated parameters tested. The mobile phase composition of .02M $K_2HPO_4$: Acetonitrile: Methanol (85:5:10 v/v/v), showed good separation and resolution. Satisfactory validation parameters such as linearity, recovery, precision LOD and LOQ were established by following ICH guidelines. Therefore, the proposed analytical procedure could be useful for regular monitoring, pharma manufacturing labs and research scholars.

## Acknowledgement

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