

# A Method Development and Validation of Rabeprazole Sodium (API) by High-Performance Liquid Chromatography

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**Abstract:** A simple and accurate methods to determine Rabeprazole sodium, in pure powder and tablet dosage form, were developed and validated using liquid chromatography (LC). The LC separation was achieved on a Inertsil ODS 3V, 150 x 4.6 mm, 5 $\mu$  in the isocratic mode using buffer : acetonitrile (65 : 35, v/v), adjusted to pH 6.00  $\pm$  0.05 with dilute KOH, as the mobile phase at a flow rate of 1.5 ml/min. the methods were performed at 280 nm; In LC method, quantification was achieved with PDA detection over the concentration range of 80 to 120  $\mu$ g/ml. The methods were validated, and the results were compared statistically. They were found to be simple, accurate, precise, and specific. The methods were successfully applied for the determination of Rabeprazole sodium in pure powder and Tablet dosage form without any interference from common excipients.

Key words: Rabeprazole sodium, PDA detection, Liquid Chromatography

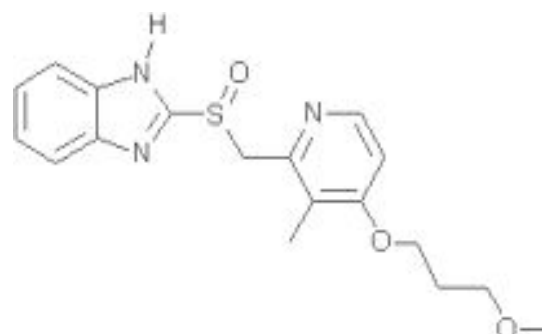
## Introduction

Rabeprazole is an antiulcer drug in the class of proton pump inhibitors. It was developed by Eisai Co. and is marketed by Janssen-Cilag as Rabeprazole sodium under the brand names Aciphex and Pariet.

Rabeprazole Sodium is delayed-release tablets, a substituted benzimidazole that inhibits gastric acid secretion. Rabeprazole sodium is known chemically as 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1H-benzimidazole sodium salt. It has an empirical formula of C<sub>18</sub>H<sub>20</sub>N<sub>3</sub>NaO<sub>3</sub>S and a molecular weight of 381.43. Rabeprazole sodium is a white to slightly yellowish-white solid. It is very soluble in water and methanol, freely soluble in ethanol, chloroform and ethyl acetate and insoluble in ether and n-hexane. The stability of Rabeprazole sodium is a function of pH; it is rapidly degraded in acid media, and is more stable under alkaline conditions. Rabeprazole Sodium is available for oral administration as delayed-release, enteric-coated tablets containing 20 mg of Rabeprazole sodium. Inactive ingredients are mannitol, hydroxypropyl cellulose,

magnesium oxide, low-substituted hydroxypropyl cellulose, magnesium stearate, ethylcellulose, hydroxy -propyl methylcellulose phthalate, diacetylated monoglycerides, talc,titanium dioxide, carnuba wax, and ferric oxide (yellow) as a coloring agent.

## Rabeprazole sodium



Rabeprazole, which is structurally related to omeprazole, is a substituted benzimidazole, and acts as a proton pump inhibitor (PPI) that suppresses gastric acid secretion through an interaction with (H<sup>+</sup>/K<sup>+</sup>)-ATPase in gastric parietal cells. Like other PPIs (omeprazole, lansoprazole and pantoprazole), rabeprazole is effective in the treatment of various peptic diseases, including gastric and duodenal ulcer, gastroesophageal reflux disease and Zollinger–Ellison syndrome [1,2].

Cytochrome P450 (CYP) 3A4 and polymorphic CYP2C19 are involved in the metabolism of PPIs [3,4]. In individuals who are poor metabolizers (PMs) of CYP2C19, the area under the concentration-time curve (AUC) of PPIs is markedly increased and the pharmacodynamic effects of PPIs (e.g. omeprazole and lansoprazole) are enhanced in comparison with those in heterozygous extensive metabolizers (EMs) or homozygous EMs [5,6]. Nonenzymatic reduction of rabeprazole to rabeprazole thioether is reported to be a major pathway in the metabolism of rabeprazole, but the contribution of CYP2C19 is considered to be smaller, compared with the metabolism of omeprazole or lansoprazole [4,7,8]. However, several recent reports have indicated that rabeprazole plasma concentrations differ significantly among the different CYP2C19 genotypes (i.e. highest in PMs, intermediate in heterozygous EMs and lowest in homozygous EMs) [9-13] and that acid inhibition by rabeprazole depends on CYP2C19 genotypic status [11-13]. In addition, rabeprazole thioether, which is formed nonenzymatically from rabeprazole, is metabolized to dimethylated thioether-rabeprazole by CYP2C19 [11]. Therefore, CYP2C19 may have an important role in the disposition of both rabeprazole and rabeprazole thioether.

Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H<sub>2</sub>-receptor antagonist properties,[12] but suppress gastric acid secretion by inhibiting the gastric H<sup>+</sup>, K<sup>+</sup>ATPase at the secretory surface of the gastric parietal cell. [14] Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric proton-pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion.

Rabeprazole Sodium tablets are enteric-coated to allow rabeprazole sodium, which is acid, labile, to pass through the stomach relatively intact. After oral administration of 20 mg Rabeprazole Sodium, peak plasma concentrations (C<sub>max</sub>) of rabeprazole occur over a range of 2.0 to 5.0 hours (T<sub>max</sub>). The rabeprazole C<sub>max</sub> and AUC are linear over an oral dose range of 10 mg to 40 mg. There is no appreciable accumulation when doses of 10 mg to 40 mg are administered every 24 hours; the pharmacokinetics of rabeprazole is not altered by multiple dosing. The plasma half-life ranges from 1 to 2 hours.

Following oral administration of 20 mg, rabeprazole is [16,17,18] and can be detected in plasma

by 1 hour. Absolute bioavailability for a 20 mg oral tablet of rabeprazole (compared to intravenous administration) is approximately 52%. The effects of food on the absorption of rabeprazole have not been evaluated.

Rabeprazole is 96.3% bound to human plasma proteins. [13]

Rabeprazole is extensively metabolized. The thioether and sulphone are the primary metabolites measured in human plasma. These metabolites were not observed to have significant antisecretory activity. In vitro[15] studies have demonstrated that rabeprazole is primarily metabolized in the liver by cytochromes P450 3A (sulphone metabolite) and <sup>2</sup>C<sup>19</sup> (desmethyl rabeprazole). The thioether metabolite is formed by reduction of rabeprazole. [19]

Following a single 20 mg oral dose of <sup>14</sup>C-labeled rabeprazole, approximately 90% of the drug was eliminated in the urine, primarily as thioether carboxylic acid; its glucuronide, and mercapturic acid metabolites.[20,21] The remainder of the dose was recovered in the feces. Total recovery of radioactivity was 99.8%. No unchanged rabeprazole was recovered in the urine or feces.

## Experimental

### Apparatus

A Shimadzu Corporation HPLC Class-VP, instrument equipped with PDA detector SPD-10-AVP, Auto injector of SIL-10-ADVP and Inertsil ODS 3V, 150 x 4.6 mm, 5μ was used. A Sartorius BP-110S (Gottingen, Germany) analytical balance, and an ultra sonic cleaner (Electrolab) were also used.

### Reagents and materials

Rabeprazole sodium reference standard (Potency : 96.3%), and Rabeprazole sodium API (Potency : 97.00%) Torrent Research Centre, (Ahmedabad, India) were given a gift sample. And provide a HPLC facility. HPLC grade acetonitrile were purchased from SDFine chemical (Ahmedabad, India). The water for LC was prepared by triple glass distillation and filtered through nylon 0.45μm-47mm membrane filter (Gelman laboratory, Mumbai, India). Potassium dihydrogen orthophosphate, orthophosphoric acid and triethylamine were procured from SD fine chemical (Ahmedabad, India) and were of analytical grade.

### Chromatographic conditions

#### LC method

Inertsil ODS 3V, 150 x 4.6 mm, 5μ, in the isocratic mode using buffer : acetonitrile (65 : 35, v/v), adjusted to pH 6.00 ± 0.05 with dilute KOH, as the mobile phase at a flow rate of 1.5 ml/min. The mobile phase was filtered through nylon 0.45μm-47mm membrane filter and was degassed before use. The elution was monitored at 280nm, and the injection volume was 20μL. Oven temp is 25°C and sample cooler temp is 4°C.

#### Preparation of buffer

Dissolve 1.75 g of monobasic potassium phosphate in 1000 ml of water and adjust the pH to 6.0 with diluted KOH.

**Preparation of mobile phase**

Prepare a filtered and degassed mixture of buffer, acetonitrile in the ratio of 65: 35.

**Preparation of diluent**

Prepare a mixture of methanol, water and diethyl amine in the ratio of 800: 200: 1 (V/V) and then adjust the pH to 10.0 with diluted O-phosphoric acid.

**Preparation of Rabeprazole sodium Standard solutions****(a) LC method**

Transfer 50 mg of Rabeprazole sodium W.standard/Ref.standard into a 100 ml volumetric flask, dissolve and dilute to volume with diluent. Further dilute 5 ml above solution to 100 ml with diluent.

**Preparation of Sample solutions**

Transfer 50 mg of Rabeprazole sodium sample to be tested into a 100 ml volumetric flask, dissolve and dilute to volume with diluent. Further dilute 5 ml of above solution to 100 ml with diluents

**Method validation****Specificity****Check for Interference from blank**

A blank, standard preparation and sample preparation (unspiked) and sample preparation (spiked) were prepared and injected. % assay of the sample preparation and the spiked sample preparation and the spiked sample preparation and peak purity index for the analyte peak in standard, sample preparation and sample preparation (spiked) were determined and record in table-1 & table-2.

**Check for interference from forced degradation study**

The Rabeprazole sodium API was subjected to acid, base, oxidation, thermal degradation and photo degradation. For each degradation, a blank was prepared separately.

A blank, stressed sample for each degradation solution were prepared and injected. The peak purity index for the main peak in all the degraded sample preparation was determined and shows in table -3.

**Calibration curve (Linearity)****(b) LC method**

Linearity was determined at five levels over the range of 80% to 120% of test concentration. A standard linearity solution was prepared to attain concentration of 80%, 90%, 100%, 110% and 120% of the test concentration. Each linearity solution was injected in duplicate. The mean area at each level is calculated and a graph of mean area versus concentration is plotted. The correlation co-efficient (r), Y-intercept, slope of regression line, residual sum of squares are calculated and recorded in Table - 4.

20 $\mu$ L of each solution were injected under the operating chromatographic conditions as described above. Calibration curves were constructed by plotting peak areas vs. concentrations of Rabeprazole sodium, and the regression equations were calculated. Each reading was average of three determinations

**Method precision (Repeatability)**

Six sample were prepared and analyzed as per method. Calculated individual assay value, % RSD all are recorded.

**Intermediate precision**

The procedure followed for method precision was repeated on a different day; by different analyst, using a different HPLC system and different column using same lot of sample. Calculated individual assay value, mean assay value, % RSD, overall % RSD are record. Calculated the difference in the assay value of method precision and intermediate precision, calculated overall % RSD and recorded. and Figure 3 shows the chromatogram obtained System suitability Chromatogram.

**Robustness**

Three sample solutions of same lot of Rabeprazole sodium shall be prepared as per method and analyzed using different chromatographic condition as below.

- (1) Change in flow rate by  $\pm 10\%$  (use flow rate 1.35 ml/min and 1.65 ml/min)
- (2) Change the minor components in the mobile phase by  $\pm 2\%$  absolute or 30% whichever is lower. (Use composition of mobile phase as
  - (A) Buffer : Acetonitrile (67 : 33)
  - (B) Buffer : Acetonitrile (63 : 37))
- (3) Change column temperature by  $+5^{\circ}\text{C}$  (Use column oven temperature  $30^{\circ}\text{C}$ )
- (4) Change in buffer pH  $\pm 0.2$  [ i.e. pH – 5.8 and 6.2]

**Stability in analytical solution**

The standard and sample solution were prepared as per method and initial assay was determined. The standard and sample solution were stored up to 48 hours at room temperature. The standard solution was reanalyzed after 24 hours and 48 hours against freshly prepared standard preparation. Results are shown in table-5. the sample preparation was reanalyzed for assay by injection after 26 hours against freshly prepared standard preparation. The assay values obtained at different time intervals were compared with the initial value and shown in table -6.

**Results and discussion****(a) LC method**

To optimize the LC parameters, several mobile phase compositions were tried. A satisfactory separation and good peak symmetry for Rabeprazole sodium was obtained with mobile phase consisting of Buffer : Acetonitrile (65: 35 v/v), adjusted to pH  $6.0 \pm 0.05$  with KOH, to obtain better reproducibility and repeatability. Quantification was achieved with PDA detection at 280 nm based on peak area. Better resolution of the peaks with clear base line separation was found (Figure 1) and (Figure 2).

**Validation of the proposed methods****Linearity**

Linear correlation was obtained between peak area and concentration of Rabeprazole sodium in the range of 80.0 to 120.00 $\mu\text{g}/\text{ml}$  for LC method. The linearity of the calibration curves was validated by the value of correlation coefficients of the regression ( $r = 0.9999$ ). Results were determined and record in table-7.

**Method Precision**

The percentage relative standard deviation (% RSD) for Rabeprazole sodium was found to be 1.03 % by LC method (Table 2). The RSD values indicate the proposed methods are repeatable. Results were determined and record in table-8.

**Intermediate Precision (Reproducibility)**

The percentage relative standard deviation (% RSD) for Rabeprazole sodium was found to be 1.19 % respectively, by LC method. The RSD values indicate the proposed methods are repeatable. Results were determined and record in table-8.

**Solution stability**

The results obtained up to 26 and 48 hours at room temperature are well within the acceptance criteria. Therefore the sample and standard is stable in solution form up to 48 hours at room temperature. Results were determined and record in table-9.

**System suitability**

Number of theoretical plates for Rabeprazole peak in standard preparation should not be less than 3000. Asymmetry for Rabeprazole peak in standard preparation should not be more than 2.0

Relative standard deviation for five replicate injection of standard preparation should not be more than 2.0%.

The data indicate that there is no significant difference between the results obtained under normal condition and varied method parameters. Therefore method is robust.

**Specificity**

There is no interference of blank with the main peak. The degradation impurities in all sample preparation are well separated from the main peak. The peak purity index for the main peak in degraded sample preparation within the acceptance criteria. Therefore, the method can be termed as specific under stressed conditions.

**Robustness**

The data indicate that there is no significant difference between the results obtained under normal condition and varied method parameters. Therefore method is robust. And all data obtained table no 10.

**Conclusion**

The system suitability parameters are well within acceptance criteria. Therefore, the system and chromatographic conditions were suitable during each validation parameter. Since the results are within acceptance criteria for all validation parameters. Therefore, the method is considered as validated and suitable for intended use. Also, the method is specific for Rabeprazole sodium API in presence of blank, therefore the method is stability indicating.

**Abbreviations**=  $\mu$ g : Microgram, mL :Mililiter,  $\mu$ L :Microliter, SD:Standard deviation, RSD : Relative Standard Deviation.

**Table 1 : Check for Interference from blank**

Solution	Peak purity index
Standard preparation	1.00000
Sample preparation ( Un-spiked )	1.00000
Sample preparation ( spiked )	1.00000

**Table 2 : Check for Interference from blank**

Sample	% Assay	Absolute Difference (%)
Sample preparation ( Un-spiked )	101.1	-----
Sample preparation ( spiked )	100.0	1.1

**Table 3: Check for interference from forced degradation study**

Solution	Name of peak	Peak purity index
<b>As Such ( Unstressed )</b>		
Sample preparation ( API )	Rabeprazole sodium	1.00000
<b>Acid Degradation ( 0.01N HCl, Immediate )</b>		
Sample preparation ( API )	Rabeprazole sodium	1.00000
<b>Base Degradation ( 0.1N NaoH, 30 min., reflux at 50°C )</b>		
Sample preparation ( API )	Rabeprazole sodium	1.00000
<b>Oxidative Degradation ( 3% H2O2, 20 min., Room temperature )</b>		
Sample preparation ( API )	Rabeprazole sodium	1.00000
<b>Thermal Degradation ( 30 hours, 50°C )</b>		
Sample preparation ( API )	Rabeprazole sodium	1.00000
<b>Photo Degradation ( 1.2 million lux hours )</b>		
Sample preparation ( API )	Rabeprazole sodium	1.00000

**Table 4 : Linearity and Range**

Sr. No.	Conc. ( % )	Average area
1	78.5	1160539
2	88.3	1273657
3	98.1	1426755
4	107.9	15566479
5	117.7	1709637
Correlation coefficient ( r )		0.9907
Slope of regression line		14194
y-intercept		34977
Residual sum of squares		359713945.8

**Table 5 : Solution stability for standard (At room temperature)**

Time	% Assay	% Difference
Initial	100	---
After about 27 hours at RT	101.7	1.7
After about 27 hours at RT	101.9	1.9

**Table 6 : Solution stability for sample (At room temperature)**

Time	% Assay	% Difference
Initial	98.7	---
After about 26 hours at RT	100.3	1.6
After about 48 hours at RT	100.1	1.4

**Table 7 : System suitability data for Specificity and Linerarity.**

Sr. No.	Limit	Area of Rabeprazole sodium for Specificity	Area of Rabeprazole sodium data for Linearity
1	---	727708	1433582
2	---	726302	1432144
3	---	726016	1431898
4	---	736855	1436346
5	---	724985	1440913
Mean	---	726373.2	1434976.6
% RSD	NMT 2.0	0.14	0.26
Asymmetry	NMT 2.0	0.90	1.08
Theoretical plates	NLT 3000	4899	4899

**Table 8 : System suitability data for Method Precision and Solution stability (Initial) and Robustness (Normal condition)**

Sr. No.	Limit	Area of Rabeprazole sodium Method Precision	Area of Rabeprazole sodium Intermediate Precision
1	---	1390129	1464298
2	---	1386163	1489644
3	---	1386394	1490498
4	---	1390939	1479995
5	---	1384649	1498521
Mean	---	1387655	1484591
% RSD	NMT 2.0	0.20	0.88
Asymmetry	NMT 2.0	1.11	0.93
Theoretical plates	NLT 3000	4403	4404

**Table-9 : System suitability data for Solution stability (at 26 and 48 hours)**

Sr. No.	Limit	Area of Rabeprazole sodium (at 26 hours)	Area of Rabeprazole sodium (at 48 hours)
1	---	1485249	1485345
2	---	1484834	1485603
3	---	1480611	1484183
4	---	1476093	1481147
5	---	1471745	1474439
Mean	---	1479706	1482143
% RSD	NMT 2.0	0.39	0.31
Asymmetry	NMT 2.0	1.14	1.08
Theoretical plates	NLT 3000	4434	4454

**Table 10 : Effect on system suitability**

Condition	System suitability Parameters			
	Theoretical plates	Asymmetry	% Assay of Sample	%RSD of replicate injections
<b>( A ) Change in flow rate</b>				
Normal condition ( 1.5 ml/min )	4603	1.11	98.3%	0.20
Change in flow rate by - 10%. (1.35 ml/min)	4720	1.08	99.3%	0.18
Change in flow rate by + 10%. (1.65 ml/min )	4079	1.08	99.4%	0.15
<b>( B ) Change in minor component in the mobile phase</b>				
Change in Acetonitrile composition by - 2% absolute M.P.-(Buffer: ACN), (67:33)	4742	1.09	98.4	0.14
Change in Acetonitrile composition by + 2% absolute M.P.-(Buffer: ACN), (63:37)	3875	1.10	98.5	0.11
<b>( C ) Change in column temperature</b>				
+ 5°C (30°C)	4968	1.09	98.2	0.09
<b>( D ) Change in buffer pH</b>				
Change in buffer pH by - 0.2 units ( pH- 5.8 )	4261	1.12	98.3	0.30
Change in buffer pH by +0.2 units.( pH- 6.2 )	4209	1.11	100.2	0.36

Sample ID :RABEPRAZOLE[D2043V]  
 Method Name :F:\HPLC289\D2043V\120407\RABEPRAZOLE API ASSAY.met  
 File Name :F:\HPLC289\D2043V\120407\289-120407-002-Rep2  
 Sequence Name :F:\HPLC289\D2043V\120407\RABEPRAZOLE API ASSAY.seq  
 Sample Description :STANDARD  
 Acquired Date :12/04/07 19:50:28  
 Vial :10002  
 Injection Volume :20µl

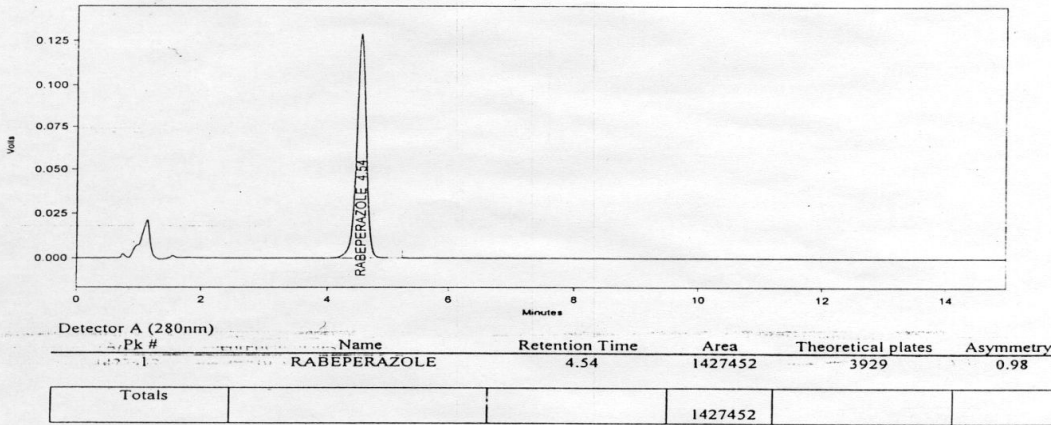


Figure 1 : Chromatogram of rabeprazole sodium standard preparation

Sample ID :RABEPRAZOLE[D2043V]  
 Method Name :F:\HPLC289\D2043V\120407\RABEPRAZOLE API ASSAY.met  
 File Name :F:\HPLC289\D2043V\120407\289-120407-003-Rep1  
 Sequence Name :F:\HPLC289\D2043V\120407\RABEPRAZOLE API ASSAY.seq  
 Sample Description :SAMPLE  
 Acquired Date :12/04/07 20:52:20  
 Vial :10003  
 Injection Volume :20µl

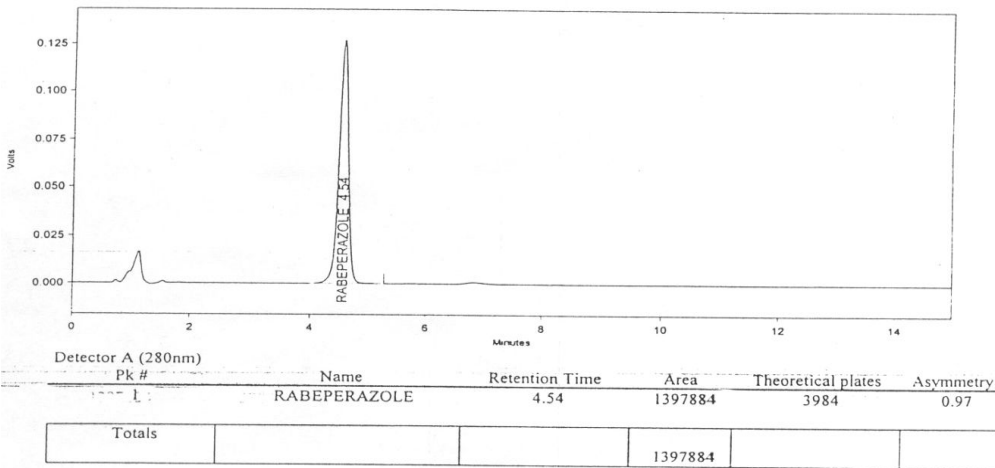


Figure 2 : Chromatogram of rabeprazole sodium sample preparation.

**Parameter: Intermediate Precision**

Sample ID :RABEPRAZOLE[D2043V]  
 Method Name :F:\HPLC289\D2043V\130407\RABEPRAZOLE API ASSAY.met  
 File Name :F:\HPLC289\D2043V\130407\289-130407-003-Rep1  
 Sequence Name :F:\HPLC289\D2043V\130407\RABEPRAZOLE.seq  
 Sample Description :INTERMEDIATE PRECISION SAMPLE 1  
 Acquired Date :13/04/07 12:15:43  
 Vial :10003  
 Injection Volume :20µl

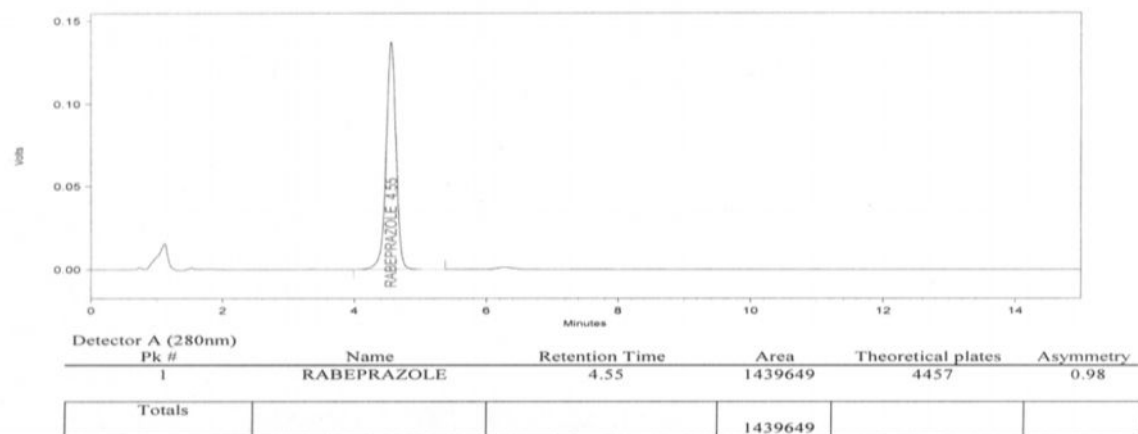


Figure 3 : Chromatogram of rabeprazole sodium intermediates precision

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