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Original Article

# Quality Control and Standardization of Rabeprazole Tablets

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## Abstract

Rabeprazole sodium is a new stable pharmaceutical composition developed by us in tablet form, consisting of rabeprazole sodium as active ingredient, excipients, a separating layer and enteric coating. The manufacturing method involves pressing with preliminary wet granulation. In this work, a method was developed for the quantitative determination of rabeprazole sodium in tablets with simultaneous determination of impurities, using high-performance liquid chromatography with diode-array detection. Chromatographic conditions were established for the separation of rabeprazole and impurities on $C_{18}$ sorbent, using mobile phase: 0.05% $K_2HP0_4$, 0.27% $KH_2P0_4$ with pH 6.8; and acetonitrile in ratio of 70:30 (v/v), using isocratic elution mode. Furthermore, a method was developed for the spectrophotometric determination of rabeprazole sodium and the conditions of its release during dissolution test were optimized. The feasibility of the developed techniques for the analysis of enteric coated rabeprazole tablets was evaluated with the following parameters: specificity, accuracy, stability of solutions, linearity, convergence, and reproducibility. The techniques were confirmed suitable for the determination of impurities in the drug and for its quantitative analysis.

*Keywords*: Dissolution test, high-performance liquid chromatography, rabeprazole sodium, spectrophotometry, tablets, quality control.

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## 1. Introduction

Benzimidazole derivatives as proton pump inhibitors constitute a prioritized pharmacological group of modern drugs and are widely used in medical practice for the treatment of various gastrointestinal diseases [1]. Among them, rabeprazole is characterized with the highest efficiency of clinical application, exhibiting long-term antisecretory

effect [2]. We have developed a new stable pharmaceutical composition in tablet form, consisting of rabeprazole sodium as active ingredient, excipients, a separating layer and enteric coating [3]. The manufacturing method involves pressing with preliminary wet granulation [3]. The separating layer protects the tablet core from free carboxyl groups present in the enteric coating, and thus, rabeprazole is effectively protected from exposure to gastric acid, enabling delivery to the intestine for optimal absorption.

For quality control of rabeprazole sodium and its dosage form, chromatographic and spectrophotometric methods [4, 5] were used. High-performance liquid chromatography (HPLC) with various types of detection is widely used in pharmaceutical analysis of rabeprazole as a universal and highly sensitive analytical method with high precision and reproducibility. However, specific analytical procedure of sample preparation and HPLC techniques, which in each case require the use of different columns, mobile phases and detectors, are frequently applied to determine rabeprazole and its permissible impurities [6].Obviously, these circumstances lead to the need to change the parameters of the chromatographic system and perform calibration each time, which at the end significantly increases the duration and cost of the whole analysis. A possible solution to this challenge is to develop optimal unified, economical and express techniques of sample preparation and chromatographic procedures.

Thus, the purpose of this study was to develop techniques for firstly, the simultaneous determination of rabeprazole and its impurities, using reversed-phase HPLC, and secondly, the spectrophotometric determination of rabeprazole when performing dissolution test on tablets of the original drug. The purpose of the study was also to perform standardization of quality parameters for a new generic drug.

## 2. Materials and Methods

The pharmaceutical formulation of rabeprazole contains 2-mercaptobenzimidazole, rabeprazolesulfone and rabeprazole sulfide (Table 1), as impurities from synthesis and decomposition [6, 7]. In the development of techniques for the determination of these impurities and quantitative analysis of rabeprazole, USP reference standards of rabeprazole sodium and its impurities were used.

The light absorbance of rabeprazole solution was determined with the spectrophotometer UV-1800 (Shimadzu, Japan), and detection was at 284 nm wavelength. Batch samples of rabeprazole tablets were studied, using HPLC (Shimadzu, Japan) with diode-array detector (SPD-M20A), Symmetry $C_{18}$ column (150 mm × 4.6 mm, 5 µm particle size), at temperature range of 18 to 25 ºC (thermostat – CTO-20AC), and automatic sample dispenser (SIL-20A). Mobile phase consisted of phosphate buffer solution (0.05% potassium monophosphate, 0.27% potassium diphosphate; pH 6.8) and acetonitrile in ratio of 70:30 (v/v); at 1 mL/min flow rate (pump – LC-20AD).

To determine the linear dependence of peak area on the concentration of rabeprazole sodium, five calibration solutions with different values of concentration were prepared and used. To do this, 0.1 g of rabeprazole sodium was placed in a 100 mL volumetric flask, dissolved in 30 mL of 0.05 M sodium hydroxide solution, and filled to the volume mark with mobile phase. Aliquots (8.0, 9.0, 10.0, 11.0, 12.0 mL) of the resulting solution were placed in 50 mL volumetric flasks, and filled to the volume mark with mobile phase. The content of rabeprazole sodium in these solutions were 80%, 90%, 100%, 110%, and 120%.

0.2 mg/mL standard solution of rabeprazole sodium was prepared as follows: 0.025 g of the analyte was dissolved in 7.5 mL of 0.05 M sodium hydroxide solution in a 25 mL volumetric flask, and filled up to the volume mark with mobile phase. 10 mL of the resultant solution was placed in a 50 mL volumetric flask, and filled up to the volume mark with mobile phase. The solution was analyzed with HPLC (n=3). It is important to note that this solution is stable for 3 hours at 5 ºC (Table 2).

Test solutions for the development of technique for the quantitative analysis of rabeprazole sodium in tablets were prepared as follows: 10 enteric coated tablets of rabeprazole (10 mg dosage), were placed in a 200 mL volumetric flask. 60 mL of 0.05 M sodium hydroxide solution was added, and the mixture was shaken for 30 min. The resulting solution was filled up to the volume mark with mobile phase, and centrifuged at $8\times10^3$ rpm for 10 min. The supernatant was filtered through a blue ribbon filter. A 10 mL aliquot of the filtrate was diluted to 25 mL with mobile phase, and filtered through a 0.45 µm filter.

The amount of rabeprazole sodium in one tablet, X was calculated by the formula:

$$X=\frac{S_1\cdot a_0\cdot P\cdot 25\cdot 10\cdot 200}{S_0\cdot 25\cdot 50\cdot n\cdot 10\cdot 100}=\frac{S_1\cdot a_0\cdot P}{S_0\cdot n\cdot 25},\ \text{g}$$

where $S_1$ – peak area of rabeprazole sodium on chromatogram of test solution;

$S_0$ – peak area of rabeprazole on chromatogram of reference standard solution of rabeprazole sodium;

$a_0$ – sample weight of reference standard of rabeprazole sodium in grams;

n – quantity of tablets taken for analysis;

P – amount of active ingredient of reference standard of rabeprazole sodium, %.

Dissolution test for rabeprazole was carried out in accordance with regulatory requirements of the Russian Federation pharmacopoeia [8] on the rotating basket dissolution apparatus; in 500 mL of two different media: 0.1 M HCl and phosphate buffer solution (pH 8.0). The rotational speed was 100 rpm. Spectrophotometric determination of analyte was carried out by measuring optical density of samples at 284 nm wavelength. Concentration of standard rabeprazole solution was 0.02mg/mL. For dissolution test in acid, due to the very low solubility and instability of rabeprazole in HCl, determination of its amount in tablet released into solution was done by calculating

the difference of the stated amount of analyte in tablet and the undissolved amount in tablet.

## 3. Results and Discussion

In the development of new techniques, the use of unified eluent provides the starting conditions of the analysis, rapid adaptation of the chromatographic system when changing the object of analysis, and is time-saving. Such eluents have proven themselves on the basis of dilute solutions of phosphoric acid and phosphate buffer solutions, owing to their small optical absorption at short wavelengths, and availability for practice. We were able to obtain separation of the components with the most acceptable selectivity in phosphoric acid and phosphate buffer solution. The best separation of rabeprazole and its impurities, taking into account peak symmetry, and efficiency of analysis as a whole, was achieved with phosphate buffer (Figure 1).

Development of technique for the quantitative analysis of rabeprazole in tablets by HPLC was carried out on model mixtures, containing rabeprazole sodium and placebo, with working concentration of 0.20 ± 0.02 mg/mL. The chromatograms of placebo solutions are shown in

Figure 2.The results of the analysis are presented in Table 3. Relative error of the average result did not exceed 2%. The amount of rabeprazolein tablets ranged from $9\times10^{-3}$ g to $1.1\times10^{-2}$ g (Table 4).

Linear dependence of peak area on the concentration of rabeprazole was observed in the range of 0.16 to 0.24 mg/mL (*Peak area* = $4.03\times10^{7}\times$*[concentration of rabeprazole]*), with correlation coefficient ($r^2 = 0.998$) (Table 5, Figure 3).

Standard solutions of rabeprazole sodium with its impurities in concentrations corresponding to their permissible content were used to check the suitability of HPLC system in the determination of impurities. The peak of rabeprazole detection was registered at 280 nm wavelength. The feasibility of the developed procedure was evaluated, using analytical parameters under optimal conditions: asymmetry factor of rabeprazole peak (≤ 2), number of theoretical plates for peak of rabeprazole (≥ 2000), resolution between the peaks of rabeprazole and 2-mercaptobenzimidazole (≥ 2), relative standard deviation of the peak area of rabeprazole (≤ 10%). The retention times for the impurities: 2-mercaptobenzimidazole, rabeprazolesulfone and rabeprazole sulfide were 3, 10 and 28 min, respectively (Figure 1). Signal linearity of the impurities was in the range of 0.05% to 1.0% of the concentration of rabeprazole in sample (*Peak area* = $3.55\times10^{7}\times$*[concentration of impurity]*), with correlation coefficient ($r^2 = 0.997$) (Table 6, 7, Figure 4, 5). The content of each impurity did not exceed 1.0%, with total impurity content not exceeding 2.5% (Table 8).

The limit of quantification (LOQ) of rabeprazole was determined by visual evaluation of its chromatograms (Figure 6, 7). The procedure for the preparation of the least concentrated rabeprazole solution is as follows:

*Solution 1*: Dissolve 25 mg of rabeprazole sodium (USP RS) in 7.5 mL 0.05 M NaOH in

a 25 mL measuring cylinder, add mobile phase to the mark and mix solution thoroughly.

*Solution 2*: Dilute 10 mL of "Solution 1" with mobile phase to 50 mL.

*Solution 3*: Dilute 1 mL of "Solution 2" with mobile phase to 100 mL.

*Solution 4 (0.1% rabeprazole)*: Dilute 1 mL of "Solution 3" with mobile phase to 10 mL.

*Solution 5 (0.05%)*: Dilute 0.5 mL of "Solution 3" with mobile phase to 10 mL. Chromatographic parameters for *"Solution 5"* are presented in Table 9.The limit of quantification (LOQ) of impurities is presented in Table 10, 11.

A novel spectrophotometric technique was developed for the quantitative analysis of rabeprazole in its dissolution test. The dissolution times were 45 min and 120 min in phosphate buffer and HCl, respectively. The dependence of optical density on rabeprazole concentration in phosphate buffer solution (pH 8.0) was linear in the range of 0.005 – 0.0120 mg/ml (*Optical density* = 37.64× *[concentration of rabeprazole]*), with correlation coefficient ($r^2$ = 0.997) (Table 12, Figure 8). The amount of analyte determined in acid medium after 2 hours was not more than 10% of its content in tablet, but was more than 95% in phosphate buffer after 45 min (Figure 9-11, Table 13-17). The absorption spectra of reference standard and test solutions of rabeprazole are presented in Figure 12.

## 4. Conclusion

The feasibility of the developed techniques for the analysis of enteric coated rabeprazole tablets was evaluated with the following parameters: specificity, accuracy, stability of solutions, linearity, convergence, and reproducibility. The techniques were confirmed suitable for the determination of impurities in the drug and for its quantitative analysis.

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**Tables:**

**Table 1.** Rabeprazole sodium and its impurities.

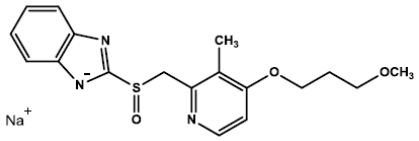
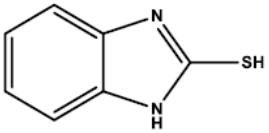
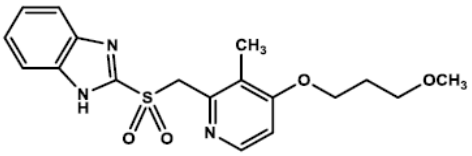
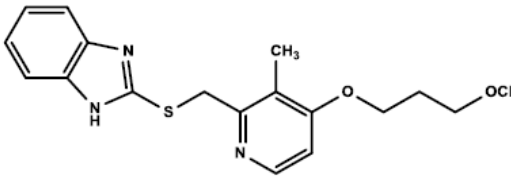
| Name | Chemical name | Structural formula |
|---|---|---|
| Rabeprazole sodium | sodium;2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl] methylsulfinyl] benzimidazol-1-ide |  |
| 2-mercaptobenzimidazole | 2-mercaptobenzimidazole |  |
| Rabeprazolesulfone | 3-methyl-4-[[((3-methoxypropoxy)-2-pyridinyl)-methyl]sulfonyl]-1H-benzoimidazole |  |
| Rabeprazole sulfide | 3-methyl-4-[[((3-methoxypropoxy)-2-pyridinyl)-methyl]thio]-1H-benzoimidazole |  |

**Table 2.** Contents of rabeprazole sodium in solution, %.

| Storage (hours) | At room temperature | | At 5 ºC | |
|---|---|---|---|---|
| | Sample solution | Standard solution | Sample solution | Standard solution |
| 0 | 99.97 | 100 | 99.99 | 100 |
| 1 | 96.16 | 100 | 99.18 | 100 |
| 2 | 94.22 | 100 | 98.67 | 100 |
| 3 | 88.52 | 100 | 98.10 | 100 |
| 4 | 80.23 | 100 | 97.15 | 100 |

**Table 3.** Accuracy of quantitative analysis of rabeprazole in model mixtures by HPLC.

| Added, g | Found | | Metrological characteristic *(P=95%,n=9)* |
|---|---|---|---|
| | g | % | |
| 0.0090 | 0.00915 | 101.67 | |
| 0.0090 | 0.00898 | 99.78 | |
| 0.0090 | 0.00905 | 100.56 | *t*-value = 2.36<br>Mean ( $\bar{X}$ )= 100.53 %<br>Dispersion ($S^2$) = 1.0413 |
| 0.0100 | 0.01016 | 101.60 | |
| 0.0100 | 0.01010 | 101.00 | Standard deviation (S) =1.02 |
| 0.0100 | 0.00998 | 99.80 | Standard deviation of mean ($S_{\bar{X}}$) = 0.3401 |
| 0.0110 | 0.01119 | 101.73 | Confidence interval ($\Delta \bar{X}$ ) = 0.8027<br>Standard error of mean ( $\bar{\varepsilon}$ ) = 0.80 % |
| 0.0110 | 0.01096 | 99.64 | |
| 0.0110 | 0.01089 | 99.00 | |

**Table 4.** Metrological characteristic of quantitative analysis of rabeprazole in tablets by HPLC (P=95%, n=5).

| Serial number | Quantity, g | Metrological characteristic | | |
|---|---|---|---|---|
| | | Standard deviation (S) | Confidence interval ($\Delta \bar{x}$ ) | Standard error of mean ( $\bar{\varepsilon}$ ), % |
| 1 | 0.0106 | 0.0105 | 0.919 | 0.78 |
| 2 | 0.0105 | 0.0104 | 0.816 | 0.79 |
| 3 | 0.0106 | 0.0104 | 0.910 | 0.81 |
| 4 | 0.0104 | 0.0101 | 0.802 | 0.80 |
| 5 | 0.0105 | 0.0101 | 0.825 | 0.78 |

**Table 5.** Dependence of peak area on rabeprazole concentration in solutions.

| Concentration of rabeprazole | | Volume of solution, ml | Peak area |
|---|---|---|---|
| mg/ml | % | | |
| 0.16 | 80 | 8.0 | 6242403 |
| 0.18 | 90 | 9.0 | 7200439 |
| 0.20 | 100 | 10.0 | 8038353 |
| 0.22 | 110 | 11.0 | 8978279 |
| 0.24 | 120 | 12.0 | 9731245 |
| Correlation coefficient = 0.9993 | | | |

**Table 6.** Dependence of peak area on rabeprazole concentration in solution (solution 3).

| Concentration of rabeprazole | | Volume of solution, ml | Peak area |
|---|---|---|---|
| mg/ml | % | | |
| 0.00010 | 10 | 0.10 | 3754 |
| 0.00020 | 20 | 0.20 | 7213 |
| 0.00050 | 50 | 0.50 | 18976 |
| 0.00075 | 75 | 0.75 | 27930 |
| 0.00100 | 100 | 1.00 | 36447 |
| 0.00125 | 125 | 1.25 | 46540 |
| 0.00150 | 150 | 1.50 | 54890 |
| 0.00175 | 175 | 1.75 | 63434 |
| 0.00200 | 200 | 2.00 | 72666 |
| Correlation coefficient = 0.99983 | | | |

**Table 7.** Dependence of peak area on rabeprazole concentration in solution (solution 4).

| Concentration of rabeprazole | | Volume of solution, ml | Peak area |
|---|---|---|---|
| mg/ml | % | | |
| 0.00010 | 5 | 0.05 | 3859 |
| 0.00040 | 20 | 0.20 | 14851 |
| 0.00100 | 50 | 0.50 | 36892 |
| 0.00150 | 75 | 0.75 | 56129 |
| 0.00200 | 100 | 1.00 | 74038 |
| 0.00250 | 125 | 1.25 | 92622 |
| 0.00300 | 150 | 1.50 | 109596 |
| 0.00350 | 175 | 1.75 | 127599 |
| 0.00400 | 200 | 2.00 | 145980 |
| Correlation coefficient = 0.99985 | | | |

**Table 8.** The content of impurities in rabeprazole tablets (n = 3).

| Impurity | Found, % | Permissible, % |
|---|---|---|
| 2-mercaptobenzimidazole | 0.094 ± 0.002 | ≤ 0.5 |
| Rabeprazolesulfone | 0.053 ± 0.001 | ≤ 0.5 |
| Rabeprazole sulfide | 0.011 ± 0.001 | ≤ 0.5 |
| Unidentified impurity | 0.048 ± 0.004 | ≤ 1.0 |

**Table 9.** Chromatographic parameters for "Solution 5".

| № | Retention time | Peak area | Peak height | № of theoretical plates | Asymmetry factor |
|---|---|---|---|---|---|
| 1 | 7.899 | 4285 | 299 | 5827.309 | 1.546 |
| 2 | 7.876 | 3909 | 291 | 6301.363 | 1.250 |
| 3 | 7.875 | 4634 | 312 | 4954.214 | 1.155 |
| 4 | 7.770 | 3509 | 279 | 6130.490 | 1.317 |
| 5 | 7.762 | 3874 | 275 | 5735.485 | 1.447 |
| 6 | 7.734 | 3711 | 274 | 5655.659 | 1.225 |
| Mean | 7.819 | 3987 | 288 | 5767.420 | 1.323 |
| Relative standard deviation, % | 0.915 | 10.222 | 5.174 | 8.115 | 11.132 |
| Maximum | 7.899 | 4634 | 312 | 6301.363 | 1.546 |
| Minimum | 7.734 | 3509 | 274 | 4954.214 | 1.155 |
| Standard deviation | 0.072 | 408 | 15 | 468.042 | 0.147 |

**Table 10.** Results of the quantification of impurities in tablets (dose = 10 mg).

| No | Content of impurities, % | | | |
|---|---|---|---|---|
| | 2-mercaptobenzimidazole | Rabeprazolesulfone | Rabeprazole sulfide | Unidentified impurity |
| 1 | 0.020 | - | 0.073 | - |
| 2 | 0.020 | - | 0.071 | - |
| 3 | 0.020 | - | 0.070 | - |
| 4 | 0.018 | - | 0.078 | - |
| 5 | 0.020 | - | 0.075 | - |
| 6 | 0.020 | - | 0.073 | - |
| 7 | 0.019 | - | 0.073 | - |
| 8 | 0.019 | - | 0.070 | - |
| 9 | 0.020 | - | 0.073 | - |
| 10 | 0.020 | - | 0.075 | - |
| Mean, % | 0.0196 | - | 0.0731 | - |
| Standard | 0.000699 | - | 0.00247 | - |

| | | | | |
|---|---|---|---|---|
| deviation | | | | |
| Coefficient of variation, % | 3.57 | - | 3.38 | - |

**Table 11.** Results of the quantification of impurities in tablets (dose = 20 mg).

| No | **Content of impurities, %** | | | |
|---|---|---|---|---|
| | 2-mercaptobenzimidazole | Rabeprazolesulfone | Rabeprazole sulfide | Unidentified impurity |
| 1 | 0.015 | - | 0.035 | - |
| 2 | 0.015 | - | 0.037 | - |
| 3 | 0.015 | - | 0.036 | - |
| 4 | 0.014 | - | 0.033 | - |
| 5 | 0.015 | - | 0.035 | - |
| 6 | 0.014 | - | 0.037 | - |
| 7 | 0.015 | - | 0.035 | - |
| 8 | 0.014 | - | 0.037 | - |
| 9 | 0.015 | - | 0.035 | - |
| 10 | 0.015 | - | 0.036 | - |
| Mean, % | 0.0147 | - | 0.0356 | - |
| Standard deviation | 0.000483 | - | 0.001265 | - |
| Coefficient of variation, % | 3.28 | - | 3.55 | - |

**Table 12.** Dependence of optical density on rabeprazole concentration in phosphate buffer solution (pH 8.0).

| Concentration of rabeprazole | | Volume of solution, ml | Optical density |
|---|---|---|---|
| mg/ml | % | | |
| 0.0050 | 50 | 1.0 | 0.190 |
| 0.0060 | 60 | 1.2 | 0.230 |
| 0.0080 | 80 | 1.6 | 0.298 |
| 0.0100 | 100 | 2.0 | 0.380 |
| 0.0120 | 120 | 2.4 | 0.448 |
| Correlation coefficient = 0.9991 | | | |

**Table 13.** Amount of rabeprazole sodium released into solution from enteric coated tablet of the drug (Buffer stage).

| № | **Release, %** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **10 mg** | | | | **20 mg** | | | |
| | **5 minutes** | **15 minutes** | **30 minutes** | **45 minutes** | **5 minutes** | **15 minutes** | **30 minutes** | **45 minutes** |
| 1 | 13.20 | 32.56 | 99.83 | 100.41 | 15.04 | 28.43 | 95.54 | 100.25 |
| 2 | 12.26 | 33.89 | 98.73 | 99.36 | 14.48 | 22.01 | 103.25 | 103.54 |
| 3 | 12.53 | 32.47 | 100.61 | 102.36 | 15.04 | 23.83 | 94.19 | 99.85 |
| 4 | 13.09 | 31.58 | 101.96 | 102.87 | 14.76 | 24.10 | 98.35 | 98.71 |
| 5 | 14.07 | 30.69 | 100.93 | 102.74 | 15.73 | 24.24 | 95.54 | 100.74 |
| 6 | 15.32 | 32.58 | 99.81 | 99.94 | 16.85 | 24.57 | 94.28 | 96.87 |
| 7 | 13.20 | 33.69 | 101.26 | 101.45 | 14.58 | 23.59 | 93.65 | 97.43 |
| 8 | 12.26 | 32.89 | 102.49 | 102.65 | 15.96 | 24.78 | 95.79 | 100.18 |
| 9 | 12.53 | 31.48 | 101.47 | 101.55 | 16.04 | 23.87 | 93.07 | 102.54 |
| 10 | 13.09 | 32.54 | 100.84 | 102.47 | 14.27 | 25.84 | 94.02 | 99.20 |
| 11 | 14.07 | 30.54 | 99.65 | 100.58 | 15.32 | 26.97 | 94.09 | 101.87 |
| 12 | 15.32 | 29.56 | 99.54 | 99.63 | 16.98 | 26.89 | 98.56 | 100.59 |
| Mean | 13.41 | 32.04 | 100.59 | 101.33 | 15.42 | 24.93 | 95.86 | 100.15 |
| Standard deviation | 1.07 | 1.30 | 1.11 | 1.30 | 0.90 | 1.79 | 2.90 | 1.95 |
| Coefficient of variation, % | 7.99 | 4.06 | 1.10 | 1.28 | 5.83 | 7.16 | 3.03 | 1.95 |

**Table 14.** Accuracy of the quantification of rabeprazole sodium (dose = 10 mg) not released into solution (Stage 1).

| № | Added, g | Found | | Metrological characteristics *(P=95%, n=9)* |
|---|---|---|---|---|
| | | g | % | |
| 1 | 0.005 | 0.00496 | 99.20 | *t*-value = 2.36 |
| 2 | 0.005 | 0.00495 | 99.00 | Mean ( $\bar{x}$) = 99.74% |
| 3 | 0.005 | 0.00502 | 100.40 | Dispersion ($S^2$) = 0.6503 |
| 4 | 0.010 | 0.01009 | 100.90 | Standard deviation (S) = 0.81 |
| 5 | 0.010 | 0.00989 | 98.90 | Standard deviation of mean ($S_{\bar{x}}$) = 0.2688 |
| 6 | 0.010 | 0.00998 | 99.80 | Confidence interval ($\Delta \bar{x}$)= 0.6344 |
| 7 | 0.012 | 0.01207 | 100.58 | Standard error of mean ( $\bar{\varepsilon}$) = 0.64% |
| 8 | 0.012 | 0.01185 | 98.75 | |
| 9 | 0.012 | 0.01202 | 100.17 | |

**Table 15.** Accuracy of the quantification of rabeprazole sodium (dose = 10 mg) released into solution (Stage 2).

| No | Added, g | Found | | Metrological characteristics *(P=95 %, n=9)* |
|---|---|---|---|---|
| | | g | % | |
| 1 | 0.005 | 0.00492 | 98.40 | *t*-value = 2.36 |
| 2 | 0.005 | 0.00509 | 101.80 | Mean ( $\bar{x}$) = 100.11% |
| 3 | 0.005 | 0.00502 | 100.40 | Dispersion ($S^2$) = 1.6603 |
| 4 | 0.010 | 0.01012 | 101.20 | Standard deviation (S) = 1.29 |
| 5 | 0.010 | 0.01015 | 101.50 | Standard deviation of mean ($S_{\bar{x}}$) = 0.4295 |
| 6 | 0.010 | 0.00993 | 99.30 | Confidence interval ($\Delta \bar{x}$)=1.0136 |
| 7 | 0.012 | 0.01208 | 100.67 | Standard error of mean ( $\bar{\varepsilon}$) = 1.01% |
| 8 | 0.012 | 0.01191 | 99.25 | |
| 9 | 0.012 | 0.01182 | 98.50 | |

**Table 16.** Accuracy of the quantification of rabeprazole sodium (dose = 20 mg) not released into solution (Stage 1).

| No | Added, g | Found | | Metrological characteristics *(P=95%, n=9)* |
|---|---|---|---|---|
| | | g | % | |
| 1 | 0.01 | 0.01019 | 101.90 | *t*-value = 2.36 |
| 2 | 0.01 | 0.00994 | 99.40 | Mean ($\bar{x}$) = 100.02% |
| 3 | 0.01 | 0.00989 | 98.90 | Dispersion ($S^2$) = 0.8451 |
| 4 | 0.02 | 0.02012 | 100.60 | Standard deviation of mean (S) = 0.92 |
| 5 | 0.02 | 0.01986 | 99.30 | Standard deviation of mean ($S_{\bar{x}}$) = 0.3064 |
| 6 | 0.02 | 0.02003 | 100.15 | Confidence interval ($\Delta \bar{x}$)= 0.7232 |
| 7 | 0.024 | 0.02387 | 99.46 | Standard error of mean ($\bar{\varepsilon}$) = 0.72% |
| 8 | 0.024 | 0.02396 | 99.83 | |
| 9 | 0.024 | 0.02415 | 100.63 | |

**Table 17.** Accuracy of the quantification of rabeprazole sodium (dose = 20 mg) released into solution (Stage 2).

| No | Added, g | Found | | Metrological characteristics *(P=95%, n=9)* |
|---|---|---|---|---|
| | | g | % | |
| 1 | 0.01 | 0.01019 | 101.90 | *t*-value = 2.36 |
| 2 | 0.01 | 0.01011 | 101.10 | Mean ($\bar{x}$) = 100.78% |
| 3 | 0.01 | 0.00980 | 98.00 | Dispersion ($S^2$) = 1.5524 |
| 4 | 0.02 | 0.02016 | 100.80 | Standard deviation (S) = 1.25 |
| 5 | 0.02 | 0.02025 | 101.25 | Standard deviation of mean ($S_{\bar{x}}$) = 0.4153 |
| 6 | 0.02 | 0.02034 | 101.70 | Confidence interval ($\Delta \bar{x}$) = 0.9802 |
| 7 | 0.024 | 0.02396 | 99.83 | Standard error of mean ($\bar{\varepsilon}$)=1.14% |
| 8 | 0.024 | 0.02412 | 100.50 | |
| 9 | 0.024 | 0.02446 | 101.92 | |

**Figures:**

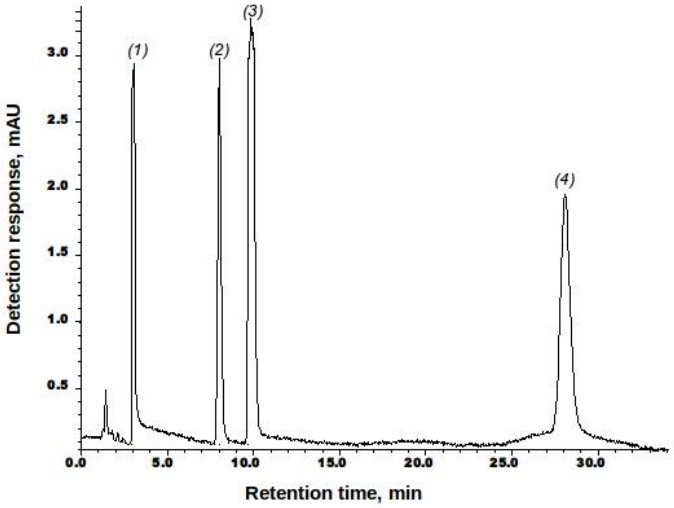



**Figure 1.** Chromatogram of rabeprazole and its impurities in phosphate buffer solution. Concentration of components is 1 µg/ mL.(1) – 2-mercaptobenzimidazole, (2) – rabeprazole, (3) – rabeprazolesulfone, (4) – rabeprazole sulfide. Chromatography conditions: mobile phase consisted of phosphate buffer solution (0.05% potassium monophsphate, 0.27% potassium diphosphate; pH 6.8) and acetonitrile in ratio of 70:30 (v/v); 1 mL/min flow rate; diode-array detection at 280 nm; Symmetry $C_{18}$ column (150 × 4.6 mm, *5 µm* particle size); temperature range of 18 to 25 ºC.

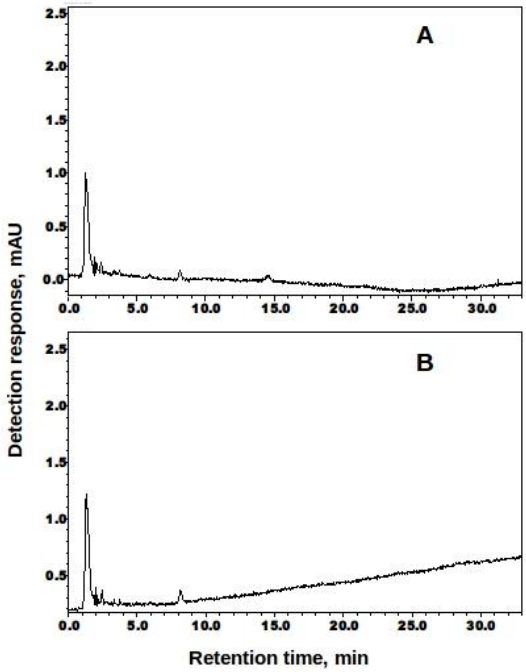



**Figure 2.** Chromatograms of placebo solutions: A – 10 mg dosage; B – 20 mg dosage. Chromatography conditions: mobile phase consisted of phosphate buffer solution (0.05% potassium monophsphate, 0.27% potassium diphosphate; pH 6.8) and acetonitrile in ratio of 70:30 (v/v); 1 mL/min flow rate; diode-array detection at 280 nm; Symmetry $C_{18}$ column (150 × 4.6 mm, *5 µm* particle size); temperature range of 18 to 25 ºC.

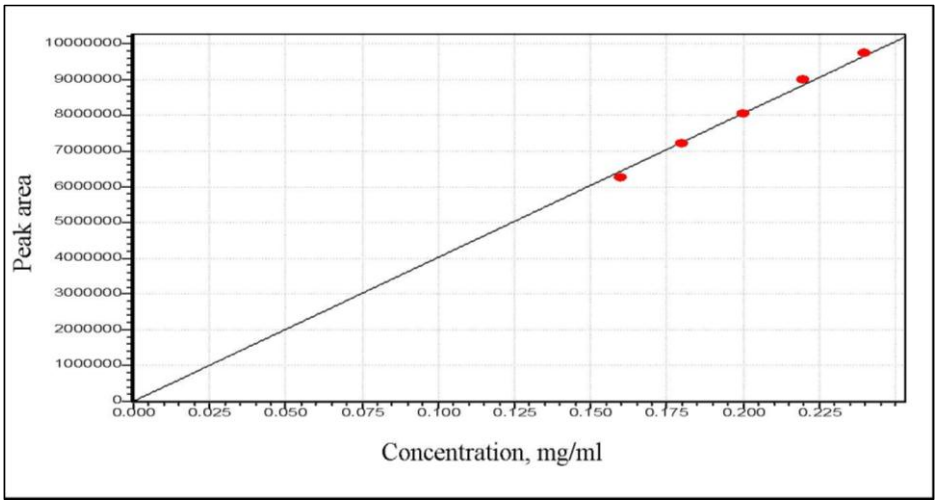



**Figure 3.** Dependence of peak area on rabeprazole concentration in solutions.

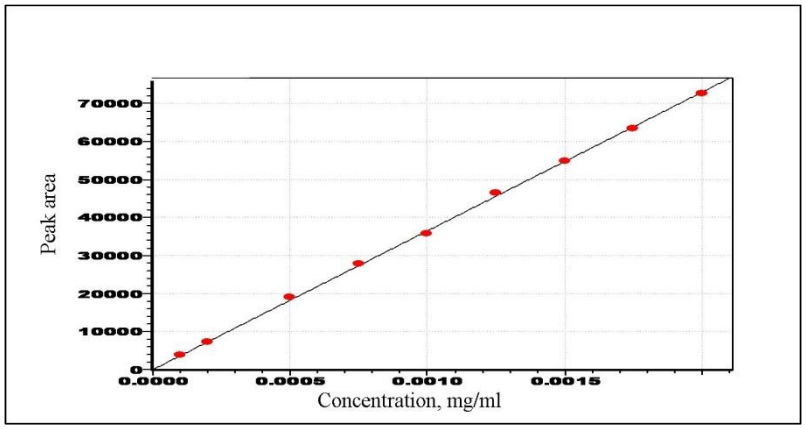



**Figure 4.** Dependence of peak area on rabeprazole concentration in solution (solution 3).

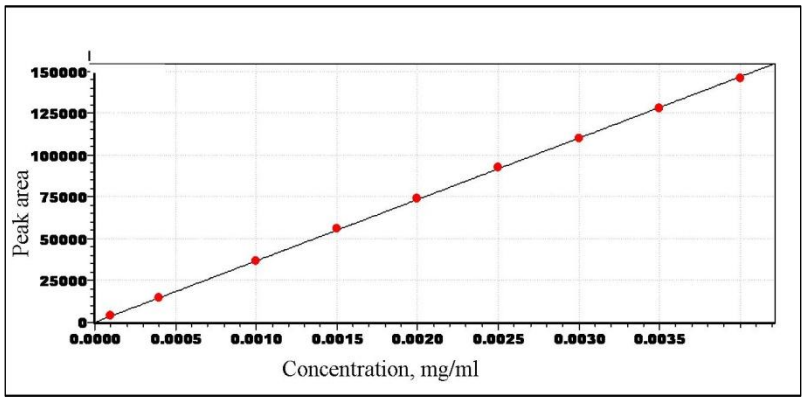



**Figure 5.** Dependence of peak area on rabeprazole concentration in solution (solution 4).

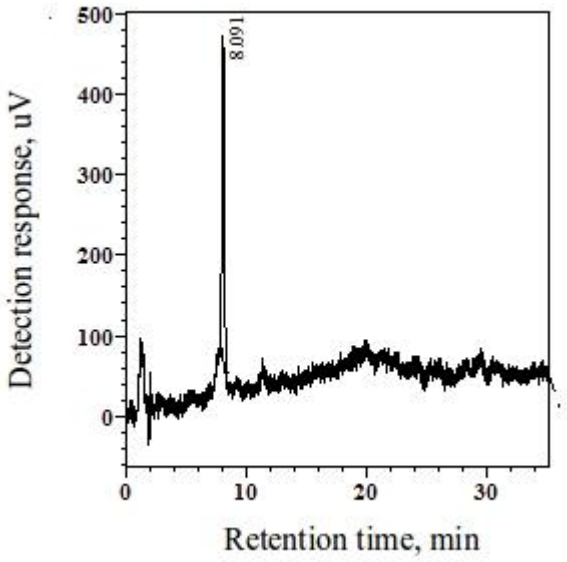



**Figure 6.** Chromatogram of *"solution 4"* (LOQ = 0.1%; Retention time = 8.091; Peak area = 5309; Peak height = 401; № of theoretical plates = 7478.337; Asymmetry factor = 1.112).

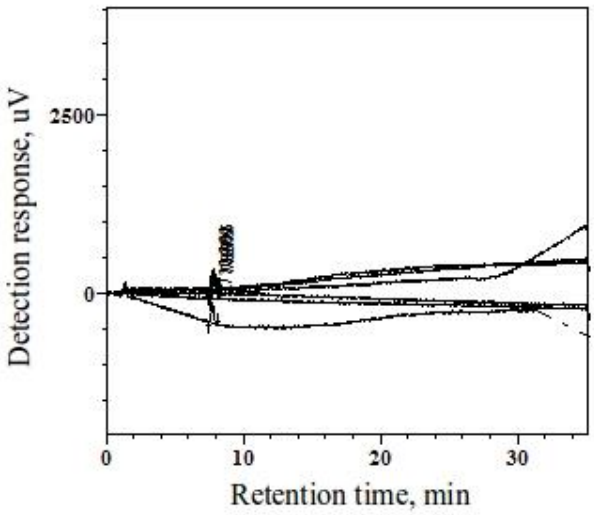



**Figure 7.** Chromatogram of "Solution 5" (LOQ = 0.05%; n=6).

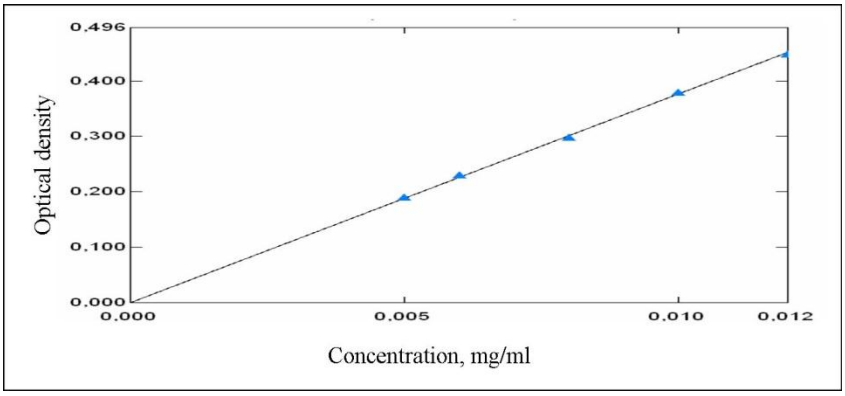



**Figure 8.** Dependence of optical density on rabeprazole concentration in phosphate buffer solution (pH 8.0).

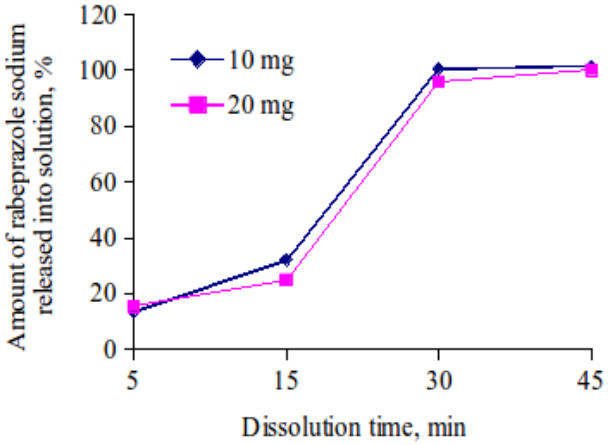



**Figure 9.** Dissolution profile of rabeprazole tablet.

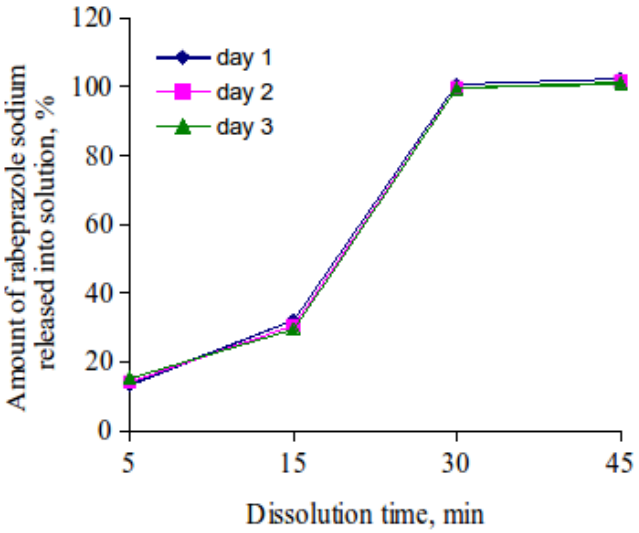



**Figure 10.** Dissolution profile of rabeprazole tablet in different days (dose=10 mg, stage 2).

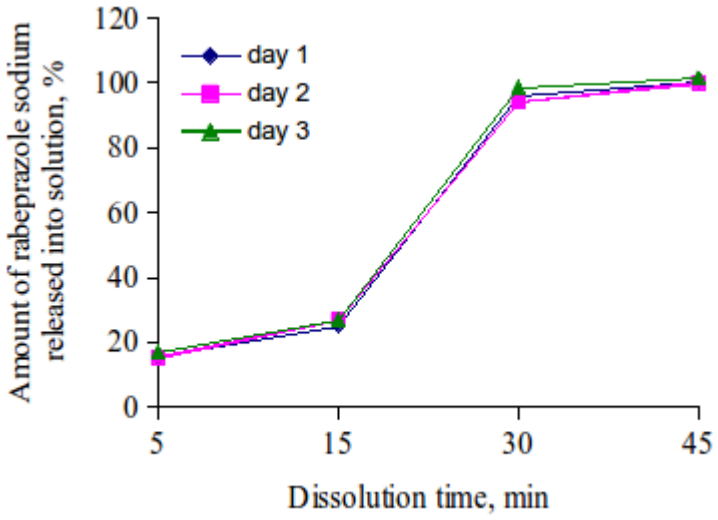



**Figure 11.** Dissolution profile of rabeprazole tablet in different days (dose=20 mg, stage 2).

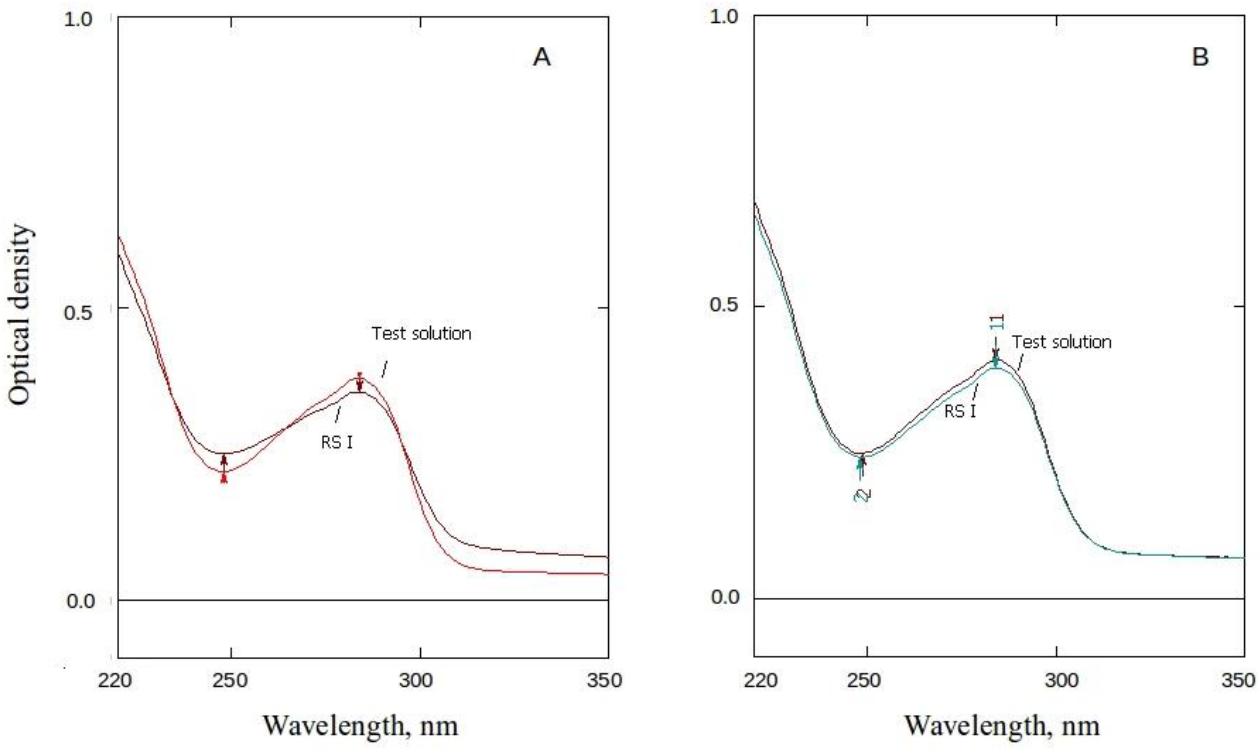



**Figure 12.** The absorption spectra of reference standard and test solutions of rabeprazole: (A) dissolution in 0.1 M HCl; (B) dissolution in phosphate buffer solution (pH 8.0). Concentration of solutions was 0.01 mg/mL.