



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 C₁₈ sorbent, using mobile phase: 0.05% K₂HPO₄, 0.27% KH₂PO₄ 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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Cite this article as: Chuvashova D, Anisimov A,
Garmonov S, Egorova S, Quality Control and
Standardization of Rabeprazole Tablets, 2020, 16 (2):
69-86.

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 C₁₈ column (150 mm × 4.6 mm, 5 μm particle size), at temperature range of 18 to 25 °C (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 °C (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 8×10^3 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 μ m 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 rabeprazole in tablets ranged from 9×10^{-3} g to 1.1×10^{-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 ($Peak\ area = 4.03 \times 10^7 \times [concentration\ of\ rabeprazole]$),

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 ($\leq 10\%$). 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 ($Peak\ area = 3.55 \times 10^7 \times [concentration\ of\ impurity]$), 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 ($Optical\ density = 37.64 \times [concentration\ of\ rabeprazole]$), 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.

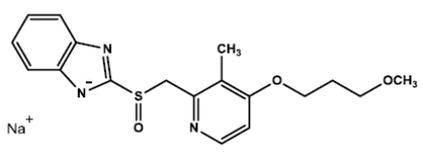
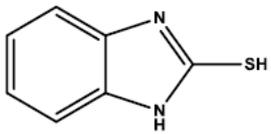
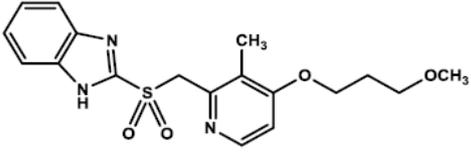
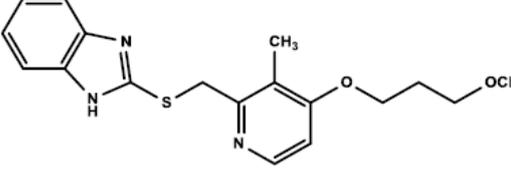
Name	Chemical name	Structural formula
Rabeprazole sodium	sodium;2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl]benzimidazol-1-ide	
2-mercaptobenzimidazole	2-mercaptobenzimidazole	
Rabeprazolesulfone	3-methyl-4-[[[(3-methoxypropoxy)-2-pyridinyl]-methyl]sulfonyl]-1H-benzoimidazole	
Rabeprazole 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 °C	
	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	t -value = 2.36
0.0090	0.00905	100.56	Mean (\bar{X}) = 100.53 %
0.0100	0.01016	101.60	Dispersion (S^2) = 1.0413
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
0.0110	0.01096	99.64	Standard error of mean ($\bar{\varepsilon}$) = 0.80 %
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 Mean (\bar{x}) = 99.74% Dispersion (S^2) = 0.6503 Standard deviation (S) = 0.81 Standard deviation of mean ($S_{\bar{x}}$) = 0.2688 Confidence interval ($\Delta \bar{x}$) = 0.6344 Standard error of mean ($\bar{\epsilon}$) = 0.64%
2	0.005	0.00495	99.00	
3	0.005	0.00502	100.40	
4	0.010	0.01009	100.90	
5	0.010	0.00989	98.90	
6	0.010	0.00998	99.80	
7	0.012	0.01207	100.58	
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 Mean (\bar{x}) = 100.11% Dispersion (S^2) = 1.6603 Standard deviation (S) = 1.29 Standard deviation of mean ($S_{\bar{x}}$) = 0.4295 Confidence interval ($\Delta \bar{x}$) = 1.0136 Standard error of mean ($\bar{\epsilon}$) = 1.01%
2	0.005	0.00509	101.80	
3	0.005	0.00502	100.40	
4	0.010	0.01012	101.20	
5	0.010	0.01015	101.50	
6	0.010	0.00993	99.30	
7	0.012	0.01208	100.67	
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:

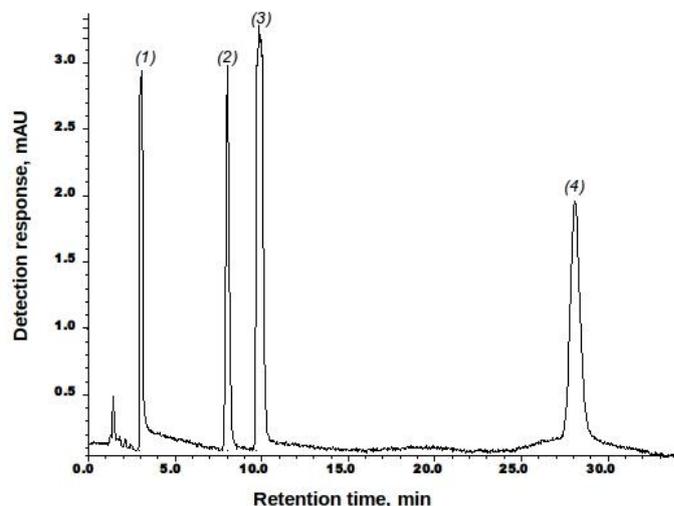


Figure 1. Chromatogram of rabeprazole and its impurities in phosphate buffer solution. Concentration of components is 1 µg/ mL. (1) – 2-mercaptobenzimidazole, (2) – rabeprazole, (3) – rabeprazolesulfone, (4) – rabeprazole sulfide. Chromatography conditions: mobile phase consisted of phosphate buffer solution (0.05% potassium monophosphate, 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 C₁₈ column (150 × 4.6 mm, 5 µm particle size); temperature range of 18 to 25 °C.

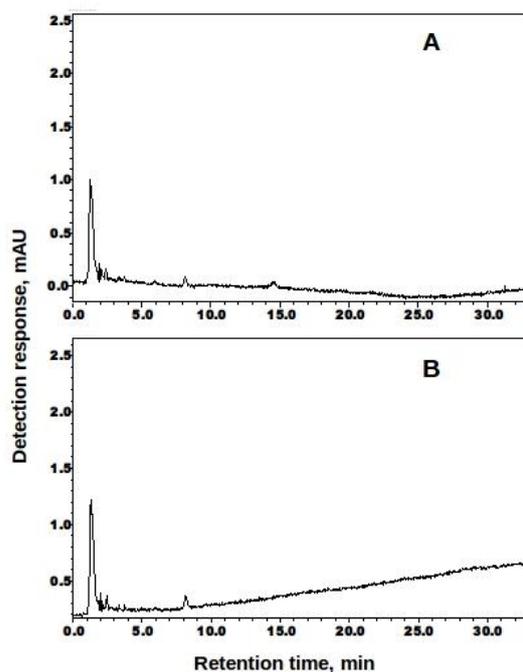


Figure 2. Chromatograms of placebo solutions: A – 10 mg dosage; B – 20 mg dosage. Chromatography conditions: mobile phase consisted of phosphate buffer solution (0.05% potassium monophosphate, 0.27% potassium diphosphate; pH 6.8) and acetonitrile in ratio of 70:30 (v/v); 1 mL/min flow rate; diode-array detection at 280 nm; Symmetry C₁₈ column (150 × 4.6 mm, 5 µm particle size); temperature range of 18 to 25 °C.

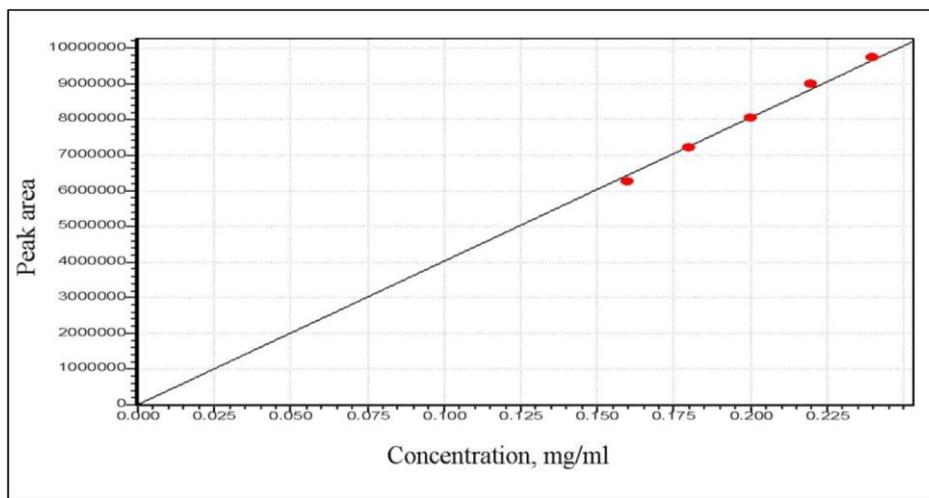


Figure 3. Dependence of peak area on rabeprazole concentration in solutions.

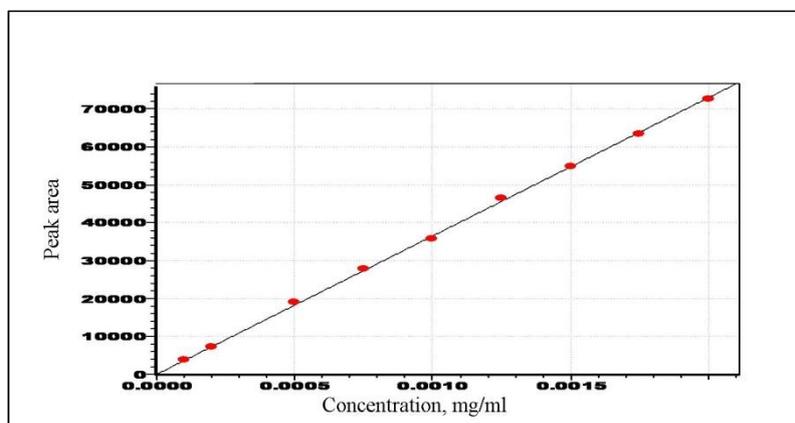


Figure 4. Dependence of peak area on rabeprazole concentration in solution (solution 3).

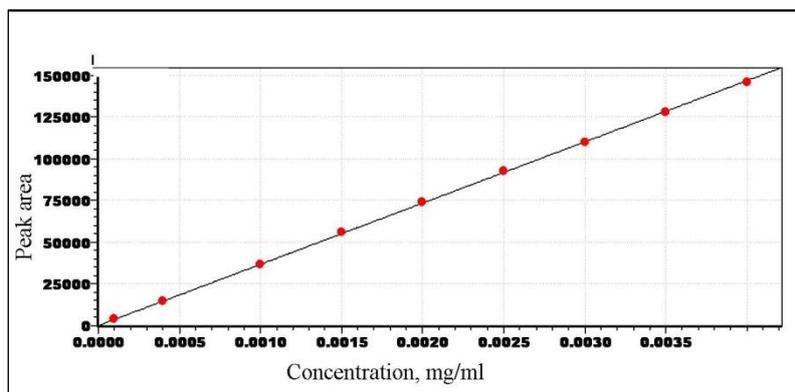


Figure 5. Dependence of peak area on rabeprazole concentration in solution (solution 4).

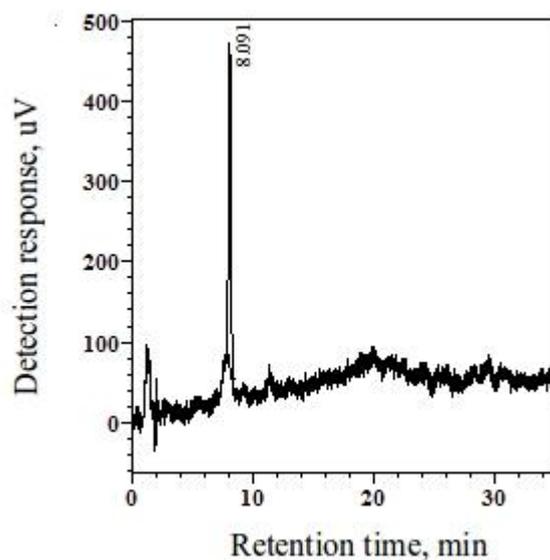


Figure 6. Chromatogram of “solution 4” (LOQ = 0.1%; Retention time = 8.091; Peak area = 5309; Peak height = 401; № of theoretical plates = 7478.337; Asymmetry factor = 1.112).

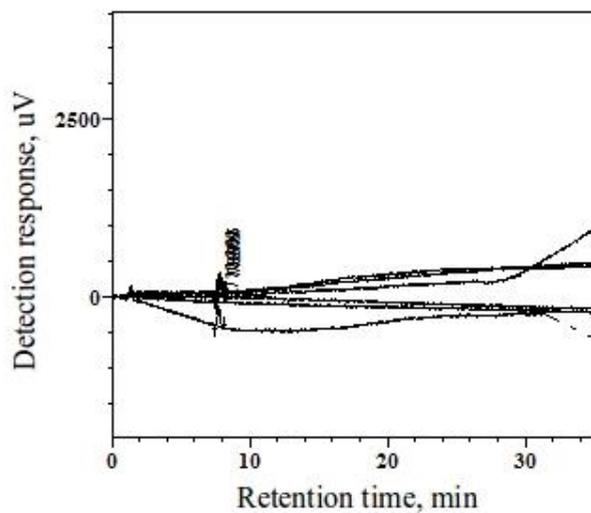


Figure 7. Chromatogram of “Solution 5” (LOQ = 0.05%; n=6).

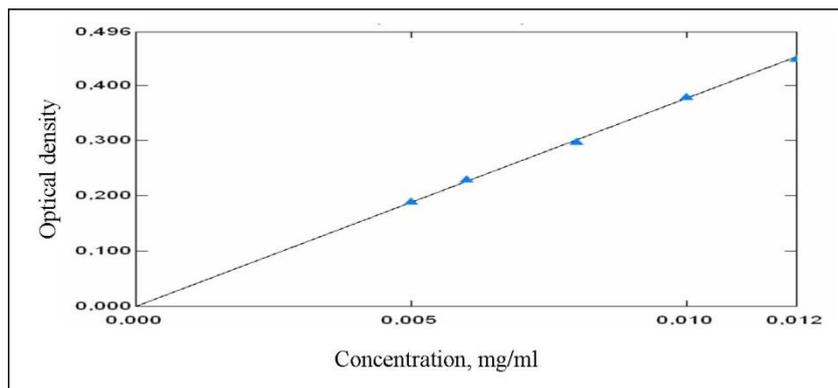


Figure 8. Dependence of optical density on rabeprazole concentration in phosphate buffer solution (pH 8.0).

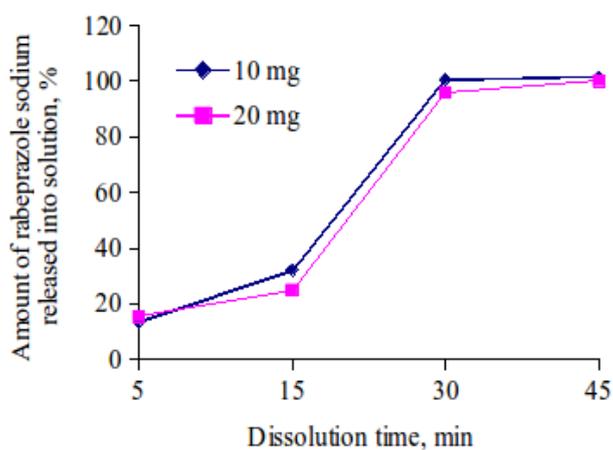


Figure 9. Dissolution profile of rabeprazole tablet.

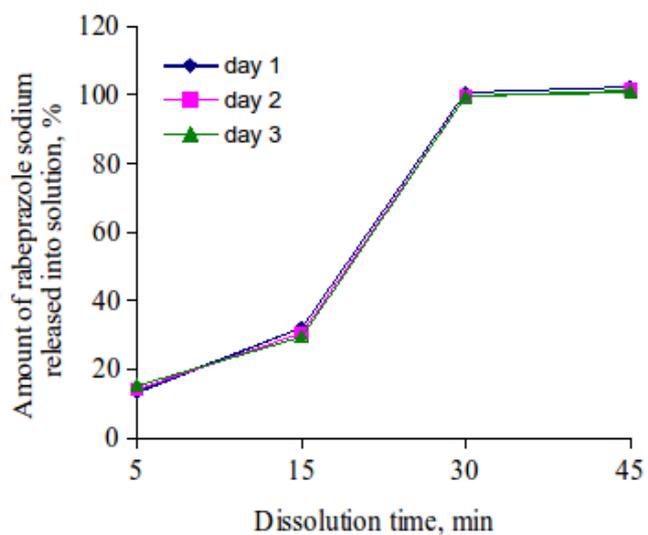


Figure 10. Dissolution profile of rabeprazole tablet in different days (dose=10 mg, stage 2).

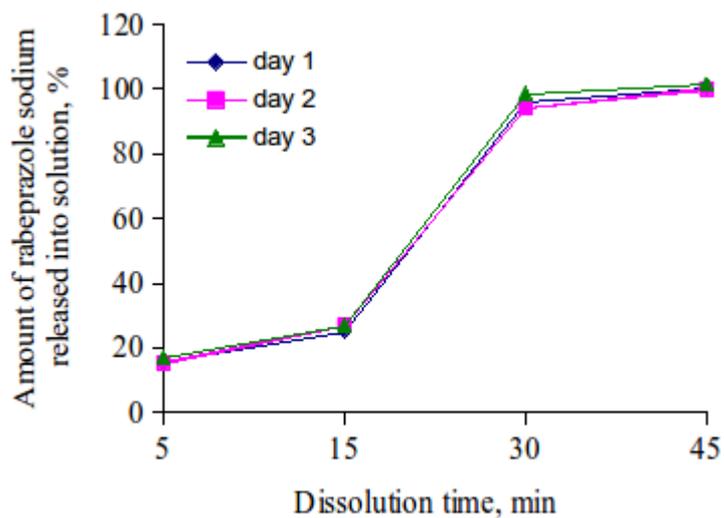


Figure 11. Dissolution profile of rabeprazole tablet in different days (dose=20 mg, stage 2).

