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Short communication

A validated stability indicating ultra performance liquid chromatographic method for determination of impurities in Esomeprazole magnesium gastro resistant tablets

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ABSTRACT

A novel gradient reversed-phase ultra performance liquid chromatographic method has been developed for quantitative determination of Esomeprazole magnesium and its seven impurities in pharmaceutical dosage forms. Chromatographic separation has been achieved on an Acquity BEH C18, 50 mm × 2.1 mm, 1.7 μm with buffered mobile phase consisting solvent A (0.04 molar (M) glycine (pH 9.0) buffer) and solvent B (mixture of acetonitrile and Milli-Q water in the ratio 90: 10 (*v/v*); respectively) delivered at flow rate of 0.21 mL min^{-1} and the detection wavelength 305 nm. Resolution of Esomeprazole magnesium and all the seven potential impurities has been achieved greater than 2.0 for all pairs of compounds. The drug was subjected to the stress conditions of oxidative, acid, base, hydrolytic, thermal and photolytic degradation. Esomeprazole magnesium was found to degrade significantly in oxidative and acid hydrolysis stress conditions and stable in base, hydrolytic and photolytic degradation conditions. The degradation products were well resolved from main peak and its impurities, thus proved the stability indicating power of the method. The stress samples were assayed against a reference standard and the mass balance was found to be close to 99.1%. So this method was also suitable for Assay determination of Esomeprazole magnesium in pharmaceutical dosage forms. The developed method was validated as per ICH guidelines with respect to specificity, linearity, limit of detection, limit of quantification, accuracy, precision and robustness.

1. Introduction

Esomeprazole magnesium belongs to a class of medicine known as proton pump inhibitors (PPIs) [1]. Its chemical designation is Bis (5-methoxy-2-[(S)-[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole-1-yl)-magnesium (Fig. 1). The seven possible related compounds (degradents and process related impurities) as imp-1 to imp-7 of Esomeprazole magnesium having chemical names are 5-Methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1′-oxide (N-Oxide), 2-Mercapto-5-methoxy benzimidazole (benzimidazole), 5-Methoxy-2-[[(4-methoxy-3,5-dimethyl pyridin-2-yl)methyl] sulphonyl]-1H-benzimidazole (Sulphone), 5-Methoxy-2-[[(3,5-dimethylpyridiny-2-yl)methyl]sulphonyl]-1H-benzimidazole (Desmethoxy), 5-Methoxy-2-[[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulphanyl]-1H-benzimidazole (Sulphide), Dihydro pyridine impurity and N-methyl impurity respectively (Fig. 1). Out of seven impurities, Imp-1, -6 and -7 are degradents, Imp-3 and Imp-5 are processes related as well as degradents and Imp-2 and Imp-4 are process related impurities.

Esomeprazole magnesium is an effective treatment for patients with gastro esophageal reflux disease (GERD), but is particularly appropriate for those suffering from persistent, recurrent GERD which can cause disruptive, long-term symptoms [2]. Esomeprazole magnesium has been demonstrated to provide enduring relief from the impact of GERD amongst patients. It is available in 20 mg and 40 mg gastro resistant morphs tablets for oral administration under the brand name of Nexium.

In the literature there are different methods including UV [3], visible [4], and derivative [5–7] spectrometry, differential scanning calorimetry [8], and HPLC [9,10] has been reported for determination of omeprazole or its sodium salt. Some of those methods are stability indicating. Official methods in USP27 [11] and BP2004 [12] are based on HPLC analysis. But no single stability indicating HPLC/UPLC method for estimation of impurities in Esomeprazole is reported till date. Hence we have developed a stability-indicating

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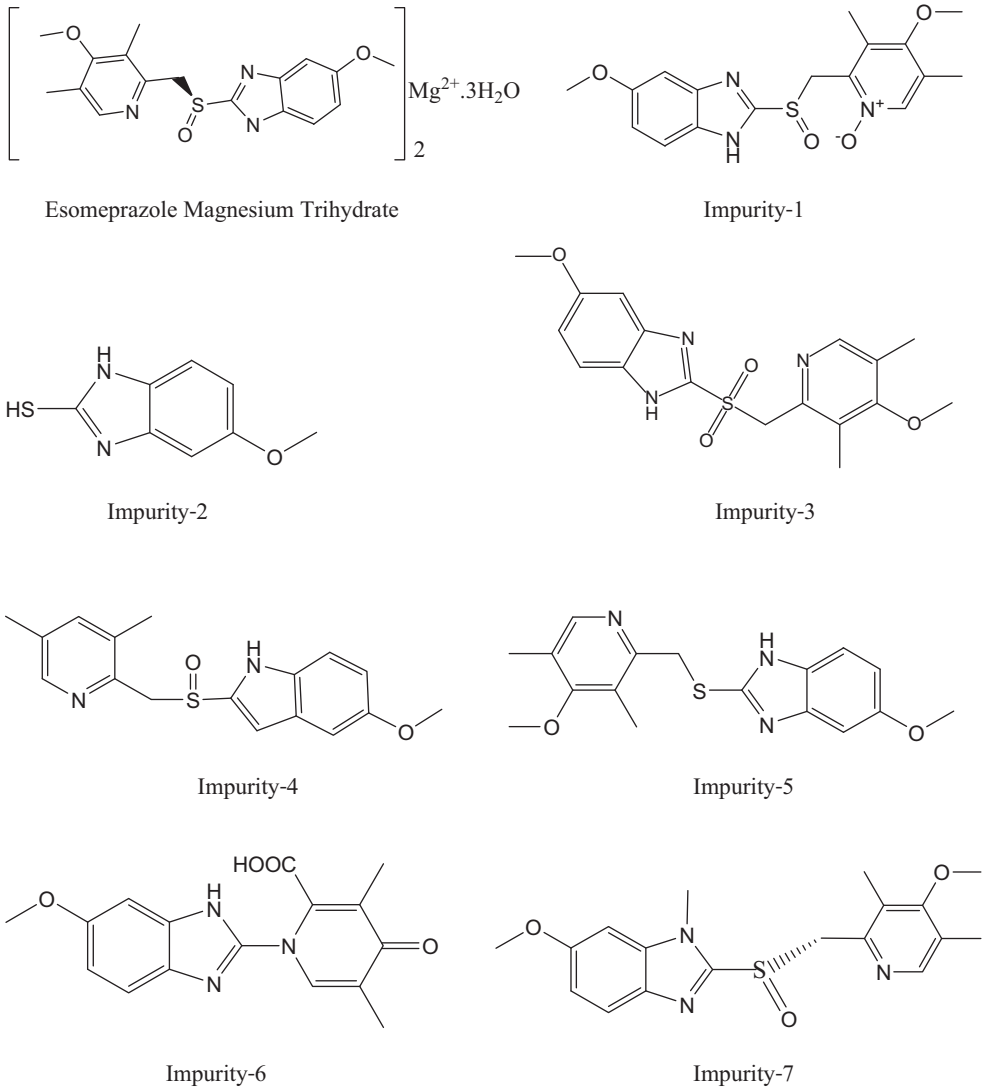

Fig. 1. Chemical structures of Esomeprazole magnesium trihydrate and its seven impurities.

RP-LC method that can separate and determine Esomeprazole magnesium and its seven impurities namely imp-1, imp-2, imp-2, imp-4 and imp-5, imp-6 and imp-7 (Fig. 2).

2. Experimental

2.1. Chemicals and reagents

All Standards and tablets were supplied by Dr. Reddy's laboratories limited, Hyderabad, India. The HPLC grade acetonitrile, methanol, and analytical grade glycene, borax and ortho phosphoric acid were purchased from Merck, Darmstadt, Germany. Water used was obtained by using Millipore MilliQ Plus water purification system.

2.2. Equipment

UPLC™ system (Waters, Milford, USA) we used consists of a binary solvent manager, a sample manager and a PDA detector. The output signal was monitored and processed using empower2 software. Cintex digital water bath was used for hydrolysis studies. Photo stability studies were carried out in a photo stability chamber (Sanyo, Leicestershire, UK). Thermal stability studies were performed in a dry air oven (Cintex, Mumbai, India).

2.3. Chromatographic conditions

The chromatographic column used was an Acquity BEH C18 50 mm × 2.1 mm 1.7 μm. The separation was achieved on a gradient method. 0.04 M glycine (pH 9.0) buffer and the mobile phase B contains a mixture of acetonitrile and Milli-Q water in the ratio 90:10 (v/v); respectively. The flow rate was 0.21 mL min^{-1} and the detection wavelength was 305 nm. The UPLC gradient program was set as: time (min)/% solution B: 0/8, 2.5/10, 5/15, 7/25, 12/40, 14/45, 16/85, 18/8, and 25/8. The column temperature was maintained at 25 °C (ambient) and the detection was monitored at a wavelength 305 nm. The injection volume was 2.8 μL. A mixture of 0.01 M borax and methanol in the proportion of 50:50 (v/v); respectively used as a solvent or diluent.

2.4. Preparation of stock solutions

A stock solution of Esomeprazole magnesium (0.6 mg mL^{-1}) was prepared by dissolving an appropriate amount in solvent

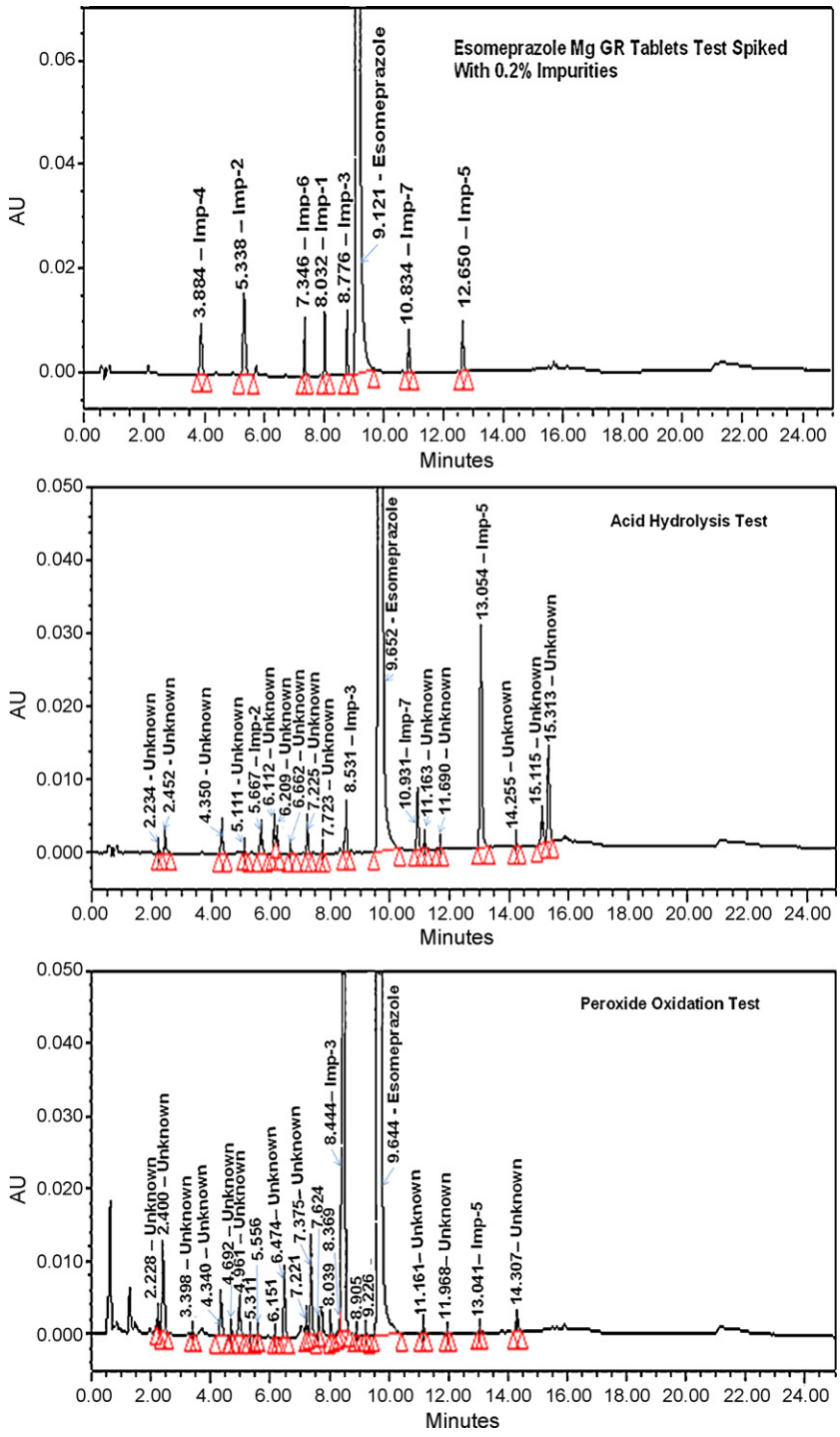

Fig. 2. Typical chromatograms of Esomeprazole magnesium test spiked with its seven impurities and forced degradation samples at optimized method conditions.

mixture. Working solutions containing 400 μg mL^{-1} were prepared from this stock solution. A mixed stock solution (0.5 mg mL^{-1}) of the impurities (denoted Imp-1 to Imp-7) was also prepared in methanol.

2.5. Preparation of system suitability solution

A mixture of Esomeprazole magnesium (0.4 mg mL^{-1}) and Imp-4 (0.0012 mg mL$^{-1)}$ was prepared by dissolving appropriate amount in solvent.

2.6. Preparation of sample solution

Tablet powder (40 mg tablets) equivalent to 40 mg drug was dissolved in solvent with rotary shaking for 10 min and sonication for 10 min to give a solution containing 400 μg mL^{-1}. This solution was filtered through a 0.45 μm pore size Nylon 66 membrane filter.

2.7. LC–MS conditions

LC–MS system (Waters 2695 Alliance liquid chromatography coupled with Quattromicro mass spectrometer with Mass Lynx

software, Waters Corporation, Milford, USA) was used for the unknown compounds formed during forced degradation and stability testing studies. The method was developed using Xteera RP8, 150 mm × 4.6 mm, 3.5 μm column as stationary phase. We have used the mobile phase containing a gradient mixture of solvents A and B. The mobile phase A is 0.04 M ammonium acetate buffer, adjusted pH 9.0 with ammonia solution. The mobile phase B contains a mixture of acetonitrile and methanol in the proportion of 85:15 (v/v). The mixture of 0.01 M borax and methanol in the proportion of 50:50 (v/v); respectively used as an extraction solvent. The gradient program (T/%B) was set as 0/6, 12/12, 17/18, 17.5/20, 30/40, 40/46, 43/85, 45/6 and 50/6 respectively prior to use, the mobile phase was mixed thoroughly and degassed. The mobile phase pumped at 1.0 mL min^{-1}. The eluted compounds Esomeprazole magnesium, Imp-1, Imp-2, Imp-3, Imp-4, Imp-5, Imp-6, Imp-7, unknown impurities and Esomeprazole magnesium were monitored at 305 nm. The run time was 50 min. The column temperature was maintained at 25 °C. The injection volumes were 40 μL. Capillary and cone voltages were 3.5 kV and 25 V, respectively. Source and dissolvation temperatures were 120 and 350 °C, respectively. Dissolvation gas flow was 650 L h^{-1}.

3. Results and discussion

3.1. Method development and optimization

The main objective of the chromatographic method was to separate closely eluting impurities Imp-4, and Esomeprazole magnesium and to elute Esomeprazole magnesium as a symmetrical peak. As we don't have much choice for selection of column in UPLC, Waters Acquity BEH C_{18} (50 mm × 2.1 mm, containing 1.7 μm particles) UPLC columns were used. As the isocratic method was not giving adequate selectivity, the gradient method containing 0.04 M glycine (pH 9.0) buffer as mobile phase A and the mobile phase B contains a mixture of acetonitrile and methanol in the ratio 85: 15 (v/v); respectively. During the fine-tuning of the method has been finalized with the gradient programs as: time (min)/% solution B: 0/6, 1.3/18, 2.2/23, 4.2/40, 6.5/75, 8.0/6, and 10/6. But during analysis of accelerated 40 °C/75% RH 6 month samples, we observed that there few unknown impurity peaks has been co-eluting with the known impurities. So in order to increase the selectivity and specificity of the method a further gradient program has been changed as: time (min)/% solution B: 0/8, 2.5/10, 5/15, 7/25, 12/40, 14/45, 16/85, 18/8 and 20/8. In order to elute highly non-polar impurities and to wash out the excipients peaks if any, the gradient program has been modified with column washing as: time (min)/% solution B: 0/8, 2.5/10, 5/15, 7/25, 12/40, 14/45, 16/85, 20/85, 20.5/8 and 25/8. So based on the formulation and composition of dosage unit one can reduce the run time to 20 min from 25 min. Again as the method gives good separation with 10 min gradient program one can use with 10 min run time if the formulation is stable enough.

Under optimized conditions Esomeprazole magnesium and the seven impurities were well separated with resolution greater than two. The relative response factor for all the seven impurities has been determined with respect to Esomeprazole (Table 1).

3.2. Validation of the method

3.2.1. Results from specificity and forced degradation studies

The specificity of a method is its suitability for analysis of a substance in the presence of potential impurities [13,14]. Stress testing of a drug substance can help identify likely degradation products, which can helps to establish degradation pathways and the intrinsic stability of the molecule. It can also be used to validate the stability-indicating power of the analytical procedures used.

The specificity of the LC method for Esomeprazole magnesium has been determined in the presence of seven impurities and degradation products. The stress conditions used for the degradation study includes light (conducted as stipulated in ICH Q1B), heat (60 °C), acid hydrolysis (0.1 M HCl at 60 °C for 1 h), basic hydrolysis (0.1 M NaOH at 60 °C for 30 min), aqueous hydrolysis at 60 °C for 30 min, and oxidation (1% H_2O_2 at 40 °C for 30 min). For studies of the effects of light the study period was 10 days whereas for heat, acidic, basic, and aqueous hydrolysis and oxidation it was 3 h. Peak purity has been checked for the Esomeprazole magnesium peak by using PDA detector in stress samples.

Assay of stressed samples has been performed by comparison with reference standard and the mass balance (% assay + % impurities + % degradation products) was calculated.

There was no peak found at the retention time of Esomeprazole magnesium and it's all seven impurities in blank and placebo blend chromatograms proves no interference from blank and placebo. Degradation was not observed when Esomeprazole magnesium has been subjected to water hydrolysis, photo, humidity and heat. Degradation was observed when the drug has been subjected to acidic hydrolysis and peroxide oxidation (Fig. 2). Esomeprazole magnesium were sensitive to acids and was degraded into Imp-2, Imp-3, Imp-5, Imp-7 and unknown impurities at RRT about 0.45, 0.75, and 1.58 by acid hydrolysis in 0.1 M HCl. This was confirmed by co-injection with Imp-2 and Imp-3, Imp-5 and Imp-7 standards. The unknown impurities formed at RRT of about 0.75 and 1.58 was not forming in real time stability study (accelerated condition up to 6 month) and need not be monitored and identified. Esomeprazole magnesium was degraded into Imp-3 (major degradation product), and unknown impurities at RRTs of about 0.25, 0.46, 0.51, 0.67 and 0.76 by oxidation with 1% hydrogen peroxide. Peak-purity test results from the PDA detector confirmed the Esomeprazole magnesium peak obtained from all the stress samples analyzed was homogeneous and pure. Peak purity results from the PDA detector for the peaks produced by degradation of Esomeprazole magnesium confirmed that all these peaks were homogeneous and pure for all the stress samples analyzed (Table 2). The mass balance for the stressed samples was close to 99% (Table 2). Assay of Esomeprazole magnesium was unaffected by the presence of the impurities/degradation products, confirming the stability-indicating power of the method.

3.2.2. Limits of detection and quantification

LOD and LOQ for the seven impurities and Esomeprazole magnesium were estimated as the amounts for which the signal-to-noise ratios were 3:1 and 10:1, respectively, by injecting a series of dilute solutions of known concentration [12]. Precision was also determined at the LOQ level by analysis of six individual preparations of the seven impurities and calculating the RSD (%) of the peak area for each impurity (Table 3).

3.2.3. Linearity

Solutions for testing linearity for the related substances were prepared by diluting the impurity stock solution to five different concentrations from the LOQ to 200% of the permitted maximum level of the impurity (i.e. the LOQ to 0.4% for Esomeprazole magnesium, Imp-1 to Imp-5, and LOQ to 1.6% for Imp-6 and Imp-7) for an analyte concentration of 400 μg mL^{-1}). The correlation coefficients, slopes, and *y*-intercepts of the calibration plots are reported. Calibration plots for the seven related substances were linear over the ranges tested. The correlation coefficients were >0.998 for all the components (Table 3). These results show there was an excellent correlation between the peak area and concentration for the seven impurities.

Table 1
Chromatographic performance data.

Compound	RT (Min)	RRT[a] ($n=3$)[d]	Resolution[c] ($n=3$)[d]	Tailing factor ($n=3$)[d]	RRF[b]
Imp-6	3.88	0.43 ± 0.18	–	1.0 ± 0.06	0.87
Imp-2	5.33	0.58 ± 0.14	11.1 ± 0.37	1.1 ± 0.00	2.91
Imp-1	7.35	0.81 ± 0.05	19.8 ± 0.77	1.1 ± 0.00	0.91
Imp-3	8.03	0.88 ± 0.06	10.8 ± 0.00	1.1 ± 0.00	0.88
Imp-4	8.78	0.96 ± 0.00	10.6 ± 0.77	1.1 ± 0.00	1.06
Esomeprazole	9.13	1.00 ± 0.00	4.2 ± 0.00	1.1 ± 3.77	1.00
Imp-7	10.84	1.19 ± 0.05	16.9 ± 0.00	1.1 ± 0.00	0.70
Imp-5	12.65	1.39 ± 0.04	16.1 ± 0.34	1.1 ± 0.00	0.87

[a] Relative retention times (RRT) were calculated against the retention time (RT) of Esomeprazole magnesium.
[b] Relative response factor were calculated against the response factor of Esomeprazole magnesium.
[c] Resolutions were calculated between two adjacent peaks.
[d] Mean ± SD.

Table 2
Stress testing (forced degradation) data.

Stress condition	Esomeprazole magnesium				Mass balance[a]
	% net Degradation	Purity angle	Purity threshold	Purity flag	
Acid hydrolysis	0.9	0.210	0.354	NO	99.5
Base hydrolysis	2.7	0.170	0.340	NO	99.4
Peroxide oxidation	11.7	0.354	0.439	NO	99.3
Water stress	0.4	0.098	0.365	NO	99.2
Photolytic-sunlight	0.08	0.099	0.365	NO	99.2
Photolytic-UV light.	0.02	0.101	0.363	NO	99.7
Heat stress	0.3	0.152	0.298	NO	99.5
Humidity stress	0.01	0.097	0.355	NO	99.6

[a] Mass balance = % assay + % impurities + % degradation products.

3.2.4. Precision

The precision of the method verified by repeatability and by intermediate precision. Repeatability was checked by (Waters Acquity UPLC™ system with PDA detector, Milford, USA) injecting six individual preparations of Esomeprazole magnesium real sample (40 mg tablets) spiked with 0.20% of its seven impurities (0.20% of impurities with respect to 0.4 mg mL^{-1} Esomeprazole magnesium). The intermediate precision of the method was also evaluated using different analyst and different instrument (Waters Acquity UPLC™ system with tunable ultraviolet detector, Milford, USA), and performing the analysis on different days. %RSD of area for each impurity was calculated for both precision as well as intermediate precision and was found within 2%. These results confirmed the precision and ruggedness of the method (Table 3).

3.2.5. Accuracy

For the impurities, recovery was determined in triplicate for 0.1, 0.15, 0.20, 0.25, and 0.30% of the analyte concentration (400 μg mL^{-1}) for Esomeprazole magnesium and Imp-1 to Imp-5 and, 0.1, 0.20, 0.80, 1.00, and 1.20% for Imp-6 and Imp-7 and recovery of the impurities was calculated (Table 4). An UPLC chromatogram obtained from a sample of Esomeprazole magnesium spiked with all seven impurities at the 0.20% level is shown in Fig. 2.

3.2.6. Robustness

To determine the robustness of the method the experimental conditions were deliberately changed and the resolution of Esomeprazole magnesium and the seven impurities was evaluated. To study the effect of flow rate on resolution it was changed to 0.19 and 0.23 mL min^{-1}. The effect of pH was studied at pH 8.8 and 9.2. The effect of column temperature was studied at 20 and 30 °C. In all these experiments the mobile phase components were not changed. The effect of the percent organic strength on resolution was studied by varying acetonitrile by −10 to +10% while other mobile phase components were held constant as stated in Section 2.3. In all the deliberate varied chromatographic conditions the selectivity as well as the performance of the method were unchanged proves the robustness of the method.

3.2.7. Stability in solution and in the mobile phase

No significant changes in the amounts of the seven impurities were observed during solution stability and mobile phase stability experiments when performed using the related substances

Table 3
Regression and precision data.

Parameter	Esomeprazole magnesium	Imp-1	Imp-2	Imp-3	Imp-4	Imp-5	Imp-6	Imp-7
LOD (μg mL^{-1})	0.02	0.024	0.016	0.024	0.024	0.032	0.044	0.028
LOQ (μg mL^{-1})	0.06	0.064	0.044	0.08	0.064	0.092	0.136	0.072
Regression equation (y)								
Slope (b)	35507.3	27706.7	110930.3	34393.8	37481.1	37767.1	28729.1	46646.8
Intercept (a)	59.4	355.6	280.7	293.7	471.2	143.8	392.2	739.4
Correlation coefficient	0.999	0.999	0.999	0.999	0.999	0.999	0.999	0.999
Precision (% RSD)[a]	1.7	1.3	1.2	1.8	1.3	1.9	1.8	1.8
Intermediate precision (% RSD)[a]	1.9	1.4	1.3	1.9	1.7	0.5	1.2	1.4
Precision @ LOQ (% RSD)[a]	2.8	2.3	1.9	2.5	2.6	2.6	2.3	2.6

Linearity range is LOQ – 200% with respect to 0.20% specification level for Imp-1, Imp-2, Imp-3, Imp-4, Imp-5 and 0.8% specification level for Imp-6 and Imp-7 individually to 0.4 mg mL^{-1} of Esomeprazole magnesium.
[a] Six determinations.

Table 4
Evaluation of accuracy.

Amount spiked[a]	% Recovery[b]							
	Esomeprazole magnesium	Imp-1	Imp-2	Imp-3	Imp-4	Imp-5	Imp-6	Imp-7
LOQ	99.9 ± 0.89	98.9 ± 1.32	98.6 ± 1.22	101.9 ± 0.33	99.9 ± 0.38	99.3 ± 0.18	98.9 ± 0.89	98.1 ± 0.32
50%	100.3 ± 1.25	99.5 ± 1.28	99.1 ± 1.23	99.5 ± 0.11	100.5 ± 0.65	99.9 ± 1.37	100.5 ± 1.25	99.1 ± 1.28
100%	99.7 ± 1.31	97.8 ± 1.42	98.9 ± 1.33	101.6 ± 0.17	99.5 ± 1.23	98.6 ± 1.39	99.3 ± 1.31	97.5 ± 1.62
150%	100.1 ± 2.0	99.7 ± 1.28	101.1 ± 1.36	98.7 ± 0.45	98.9 ± 1.29	100.5 ± 1.19	100.1 ± 1.15	99.1 ± 1.28

[a] Amount of five impurities spiked with respect to 0.20% specification level for Imp-1, Imp-2, Imp-3, Imp-4, Imp-5 and 0.8% specification level for Imp-6 and Imp-7 individually to 0.4 mg mL^{-1} of Esomeprazole magnesium.
[b] Mean ± % RSD for three determinations.

method. The results from solution stability and mobile phase stability experiments confirmed that standard solutions and sample were stable for up to 24 h during determination of related substances. The mobile phase was stable up to 48 h.

4. Conclusions

The rapid gradient RP-UPLC method developed for quantitative analysis of impurities of Esomeprazole magnesium present in pharmaceutical dosage forms is precise, accurate, linear, robust, rugged and specific. Satisfactory results were obtained from validation of the method. The method is stability-indicating and can be used for routine analysis of production samples and to check the stability of Esomeprazole magnesium dosage forms. The developed LC–MS method can be used for identification of *m*/*z* ratio of unknown impurities as well as conformation of known impurities or degradents formed during stability testing.

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