



Simultaneous Determination of Sodium, Potassium and Magnesium Counter Ions in Three Drugs: Pantoprazole Sodium, Losartan Potassium and Omeprazole Magnesium by Ion Chromatography

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The present analytical method was developed for single determination of three counter ions in pantoprazole sodium, losartan potassium and omeprazole magnesium drug substances by ion chromatography. The ion chromatography method was unique and suitable for three drugs such as pantoprazole sodium, losartan potassium and omeprazole magnesium with specification limits 5.7, 8.5 and 3.3 % of percentages of sodium, potassium and magnesium counter ions, respectively. The method was developed with Metrosep C₄ (150 × 4.0 mm, 5 μ) column and combination of 4.0 mM nitric acid, 0.1 % dipicolinic acid and 10 % acetonitrile with flow of 1 mL. The injection volume used for this analysis was 20 μL with conductivity detector. The validation was performed to single ion chromatography method for three counter ions such as sodium in pantoprazole sodium, potassium in losartan potassium and magnesium in omeprazole magnesium. The % RSD for the method precision and intermediate of sodium in the pantoprazole sodium was 1.6 % and 1.6 %, respectively. The correlation coefficient for the linearity parameter of the sodium in the pantoprazole sodium was 1.000. The accuracy of sodium in pantoprazole sodium was observed as 97, 101 and 103 % recovery at 50, 100 and 150 %, respectively. The % RSD for the method precision and intermediate of potassium in the losartan potassium was 2.0 % and 1.5 %, respectively. The correlation coefficient for the linearity of the potassium in the losartan potassium was 0.999. The accuracy of potassium in losartan potassium was observed as 97.2, 100.0 and 101.8 % recovery at 50, 100 and 150 %, respectively. The % RSD for the method precision and intermediate precision of magnesium in the omeprazole magnesium was 1.7 and 2.0 %, respectively. The correlation coefficient for the linearity of the magnesium in the omeprazole magnesium was 1.000. The accuracy of magnesium in omeprazole magnesium was observed as 113.1, 98.5 and 98.5 % recovery at 50, 100 and 150 %, respectively. The robustness study was performed for flow of mobile phase from the actual flow and acetonitrile concentration. All the robustness values were less than the 10 % of initial counter ion content. The developed and validated method can be used for the simultaneous determination of sodium, potassium and magnesium counter ions in pantoprazole sodium, losartan potassium and omeprazole magnesium, respectively.

Keywords: Pantoprazole sodium, Losartan potassium, Omeprazole magnesium, Counter ions, Validation, Ion chromatography.

INTRODUCTION

The cationic counter ions are useful for the stability of pharmaceutical drug substances and drug product. As per the ICH Q1, the stability of the drug substance and drug product will be varying by not only the chemical entity of drug substances and also the counter ions or the excipient [1]. The cations

such as sodium, potassium, magnesium and calcium, generally can be used for the stability of the active pharmaceutical ingredients and also to show different biological activities, [2]. The different ratios of inorganic counter ions (Na, Mg, Li, K and Ca) of drug substance will give different polymorphs [3]. The ratios of counter ion in the drug need to be known for the potency of drug substance and activity of drug substances [4]. The

present study describes determination of sodium in pantoprazole sodium, potassium in the losartan potassium and magnesium in the omeprazole magnesium. The pantoprazole sodium is name of sodium; 5-(difluoromethoxy)-2-[(3,4-dimethoxy-pyridin-2-yl)methylsulfinyl]benzimidazol-1-ide (Fig. 1). It inhibits the gastric acid secretion, it is a proton pump inhibitor helps to cure the ulcers, gastroesophageal reflux disorder (GERD), erosive esophagitis and Zollinger-Ellison syndrome. It is functioning by blocking acid production in the stomach. The percentage of sodium in pantoprazole sodium is 5.7. The sodium amount needs to quantify in the pantoprazole sodium drug to calculate the potency of drug substance. Losartan potassium is the potassium; [2-butyl-5-chloro-3-[[4-[2-(1,2,3-triaza-4-azanidacyclopenta-2,5-dien-5-yl)phenyl]-phenyl]-methyl]imidazol-4-yl]methanol (Fig. 1). The losartan potassium is angiotensin-II-receptor antagonist used for the treatment of hypertension and heart failure. It decreases sodium excretion, increases potassium excretion and acts as a vasoconstrictor in vascular muscle [5,6]. The percentage of potassium in losartan potassium is 8.5. The potassium amount needs to quantify in the omeprazole magnesium drug to calculate the potency of drug substance. Omeprazole magnesium is magnesium; 6-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]-1*H*-benzimidazole (Fig. 1), it uses for treatment of dyspepsia, peptic ulcer disease, Laryngopharyngeal reflux, Zollinger-Ellison syndrome and gastro oesophageal reflux diseases [7]. The percentage of magnesium in omeprazole magnesium is 3.3. The magnesium amount needs to quantify in the omeprazole magnesium drug to calculate the potency of drug substance. Several ion chromatographic methods were available to determine the cations in environmental samples and food samples [8-17] but no method was reported for counters ion in the drug substances of pantoprazole sodium losartan

potassium and omeprazole magnesium by ion chromatography. Many high performance chromatography and mass spectrometry methods were available for determination of drug substance as pantoprazole [18-27], losartan [27-35] and omeprazole [36-47].

The present work also describes the counter ions contribution in pantoprazole sodium, losartan potassium and omeprazole magnesium drug substances by ion chromatography technique. The single ion chromatography method was developed for the determination of sodium, potassium and magnesium in respective drug substances of pantoprazole sodium, losartan potassium and omeprazole magnesium. The ion chromatography method was validated against the ICHQ2 (R1) and USP analytical method validation procedures [48-50]. The other conventional and instrumental methods were used for determination sodium, potassium and magnesium in water and other type samples but they are more time taking procedure with high sample quantity, lengthy and more unsafe procedures [51-56]. The authors developed and validated ion chromatography technique requires less than 1 µg of sample for analysis and universally accepted chromatograms.

EXPERIMENTAL

Analytical grade acetonitrile was purchased from the Avancar Performance Material Mumbai, India. Analytical grade sodium chloride, potassium iodide and magnesium iodide was purchased from the Sigma Aldrich Merck Mumbai, India. The analytical grade nitric acid purchased from Qualigens fine chemicals, Mumbai, India. 1,4-Dipicolinic acid was purchased from S.D. Fine Chemicals, Mumbai, India. High pure water was collected from a Millipore Milli-Q Water purification system (Millipore, Milford, MA, USA). The drug substances of pantoprazole sodium, losartan potassium and omeprazole magnesium for research obtained from Dr. Reddy's Laboratories Ltd., Hyderabad, India.

Equipment: The complete study was performed with the Metrohm ion chromatographic system with Magic Net 3.2 software. The instrument was purchased from the Metrohm Ltd.CH-9101 Herisau, Switzerland. It is equipped with 818 IC Pump, 833 liquid handling unit, sampling injector loop is 20 µL loop, 820 IC separation centre and conductivity detector. The dilutions were performed by using gastight syringes. The polypropylene vials were used for injecting the samples, these are provided by Metrohm.

Method development and optimization of ion chromatographic method: The chromatographic conditions were optimized by using different mobile phase ratios such as acid concentrations, different buffer concentrations, different solvent concentrations (acetonitrile and acetone), different ratio of diluent (ratios of acetonitrile and water), different injection loop volumes (10, 20, 50 and 100 µL), different columns and different flow rates (0.7 mL 1.0 mL).

Standards and sample preparations: Standards preparations counter ion at specification level.

Preparation of standard stock solution of sodium: Weigh about 25 mg of sodium chloride in 100 mL volumetric flask containing the diluent and made up to the mark with diluent and sonicate to dissolve the standard.

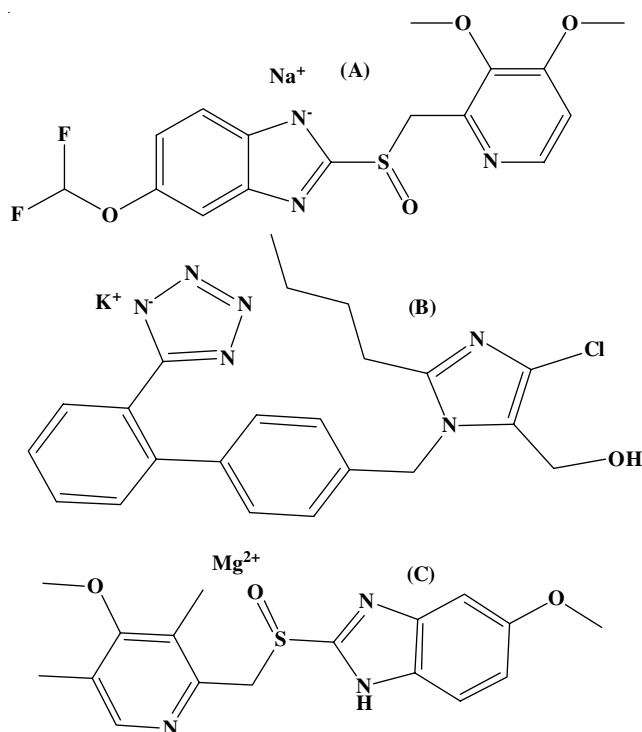


Fig. 1. Selected API's (A) Pantoprazole sodium (B) Losartan potassium (C) Omeprazole magnesium

Preparation of standard stock solution of potassium:

Weigh about 40 mg of Potassium iodide in 100 mL volumetric flask containing the diluent and made up to the mark with diluent and sonicate to dissolve the standard.

Preparation of standard stock solution of magnesium:

Weigh about 100 mg of magnesium iodide in 100 mL volumetric flask contain the diluent and made up to the mark w it diluent and sonicate to dissolve the standard.

Preparation of premixed standard solution at counter ion specification level: Transfer the 10 mL of each sodium, potassium and magnesium stock solution into the 100 mL volumetric flask and make up to the mark with diluent, cyclomix to dissolve standard solution.

Sample preparations**Preparation of stock solution (pantoprazole sodium):**

Weigh about 25 mg of pantoprazole sodium and transferred into the 25 mL volumetric flask and made up to the mark with diluent and sonicate to dissolve the sample.

Preparation of stock solution (losartan potassium):

Weigh about 100 mg of losartan potassium and transferred into the 50 mL volumetric flask and made upto the mark with diluent and sonicate to dissolve the sample.

Preparation of stock solution (omeprazole magnesium):

Weigh about 25 mg of omeprazole magnesium and transferred into the 25 mL volumetric flask and made up to the mark with diluent and sonicator to dissolve the sample.

Preparation of premixed sample solution at counter ion specification level: Transfer the 5 mL of each pantoprazole sodium, losartan potassium and 7.5 mL of omeprazole magnesium sample stock solution into the 25 mL volumetric flask and make up to the mark with diluent and cyclomix to sonicate the standard solution.

Method for determination of sodium, potassium and magnesium counter ions in drug substances: After optimized chromatographic conditions, the flow of mobile phase stabilized to run until neat base line. Injected the two diluent (water) injection followed by the five mixed standards of sodium, potassium and magnesium at counter ion specification level. Once the five injections were run, calculate the % RSD for the area of respective counter ions.

$$\text{RSD (\%)} = \frac{\text{Standard deviation of five standards}}{\text{Average area of five standards}} \times 100 \quad (1)$$

Once five standards were run, calculate the % RSD. Those should be within the 10 % the injected diluted samples (each pantoprazole sodium, losartan potassium and omeprazole magnesium sample). Record the response of the each ion from mixture of sample solution. The following formula has been used to determine the percentage of counter ion in mixed sample solution. This procedure has been applied for individual drug substance also.

$$\text{Na/K/Mg (\%)} = \frac{\text{TSA} \times \text{TSW} \times \text{SD} \times \text{CF}}{\text{SA} \times \text{SW} \times \text{SD}} \times \text{Potency} \quad (2)$$

where: TSA: Test sample area, TSW: Test sample weight, SW: Sample weight, SD: Sample dilution, SA: Standard area, C.F: Correction Factor of standard. Potency: standard potency.

Validation of ion chromatographic method:

The developed method was validated as per the ICH Q2 (R1) guideline and USP general chapter-1225: Validation of compendial procedure for the validations parameters such as precision, accuracy, linearity, range, robustness, specificity, solution stability and mobile phase stability.

Precision: Precision for developed method was performing as method precision and intermediate precision. Method precision was performing with same sample with six different specification level preparation solution. The content of each solution evaluated and calculated the coefficient variation. Similarly different day with different column, different mobile phase used for the intermediate precision and evaluated the coefficient variation. Three concentrations were studied for % RSD *i.e.* 50, 100 and 150 %.

Accuracy: Accuracy is difference between the observed the per cent of counter ions and with calculated value of ions in drug substance. This was studied by choosing the three concentrations like 50, 100 and 150 %, calculated the content of each solution. The per cent recovery was calculated with method precision solution. The following formula was used to determine the % recovery of counter ion in the drug substance.

$$\text{Recovery (\%)} = \frac{B - A}{C} \times 100 \quad (3)$$

where: B: amount of counter ion in spiked sample; A: amount of counter ion in as such sample; C: amount of counter ion in standard.

Linearity and range: The seven series of standards were used to determine the linearity range. From this range, the counter ion can be determined. The calibration curve was determined by drawing the graph between the concentration on 'X' axis and area on the 'Y' axis. The correlation coefficient, intercept, slope and STEYX were calculated.

Robustness: For performing the robustness parameter, the actual method parameters varied such as flow varied ± 10 % from the actual flow, buffer concentration ± 10 % varied from actual, the solvent concentration ± 10 % varied from actual, flow ± 10 % from actual, the solvent concentration ± 10 % varied from actual and acid concentration ± 10 % varied from actual, the acid ± 10 % varied from actual. The retention times, the coefficient variation was calculated.

Specificity: Specificity was performed by injecting the other counter ions. The other counter ions were specify with the determined counter ions, the retention times, the areas of the three ions were evaluated in presence of other counter ions.

Solution stability and mobile phase stability: The sample solution stability and mobile phase stability were performed for the 3 day (72 h). The variations of counter ions content from the initial contents were evaluated. The stored test sample was injected by 0, 12, 24, 48 h and 72 h. Interval and calculated the % difference between initial and each interval, similarly fresh was used in store the mobile phase. The % difference contents were evaluated by storing the mobile phase and injecting sample by 0, 12, 24, 48 and 72 h intervals. The following formula was used to calculate the solution stability.

$$\frac{\% \text{ Variation of counter ion in solution}}{\text{Mobile phase stability}} = \frac{\text{FC}}{\text{IC}} \times 100 \quad (4)$$

where FC: amount of counter ion at different intervals sample (e.g. 12, 24, 48 and 72 h); IC: amount of counter ion in initial sample.

RESULTS AND DISCUSSION

Method development and optimization single counter ion chromatographic method: The initial method development has been started with the Metrosep C₄ (150 × 4.0 mm, 5 μm column and 3.0 mM HNO₃ in Milli-Q water:acetone (95:5 %) mobile phase. The flow used for separation was 0.9 mL/min and run time was 20 min. The injection loop volume was 20 μL and the diluent concentration was 50:50 % of the acetonitrile and water. The magnesium eluted was about 11.12 min and the base line was with full of noise in conductivity detector with these method conditions (Fig. 2).

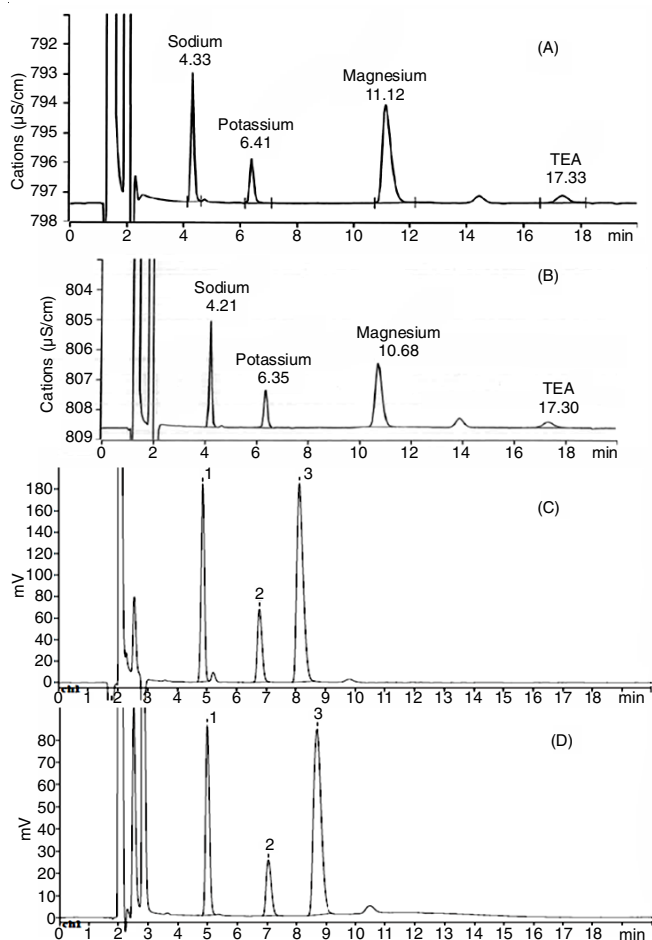


Fig. 2. Typical method development chromatograms (A) Method development trial-1 (B) Method development trial-2 (C) Method development trial-3 (D) Method development trial-4

In the second trial, the acetone was replaced with the acetonitrile by keeping remaining all conditions similar; the magnesium peak was still not good than previous trial. This was due to acetonitrile in presence of 3 mM nitric acid (Fig. 2). In the third trial, the nitric acid mobile phase replaced with 4.0 mM tartaric acid + 0.75 mM dipicolinic acid in water and 10 % acetonitrile; the flow used in this trial was 1.0 mL/min. The column used in this trial was Metrosep C₄ 250 × 4.0 × 250 mm × 5.0 μm. The run time was 20 min and injection loop

volume was 20 μL. The concentration of counter ions was 25, 25, 100 μg/mL of sodium, potassium and magnesium, respectively. All these peaks were eluted early when compared to the second method development trail because selection of mixture of two weak buffers (Fig. 2). Hence in the fourth trial, the mixer of strong and weak buffer along with organic solvent used, The column used in this trail was C₄ 250 × 4.0 × 250 mm × 5.0 μm and the mobile phase was 3 mM nitric acid, 0.1 mM dipicolinic acid in water and 10 % acetonitrile. The injection loop volume was 20 μL. The flow used for separation was 1.0 mL.

Method optimized final chromatographic conditions:

After method development, the method was evaluated for the optimization of ion chromatographic conditions and validation has been done as per the ICHQ2 (R1). The chromatographic conditions were the column of C₄ 250 × 4.0 × 250 mm × 5.0 μm, Mobile phase as 3 mM nitric acid and 0.1 mM dipicolinic acid mixed buffer 90 % and acetonitrile 10 %. The flow of mobile phase used for separation was 1.0 mL/min; the loop volume was 20 μL for the standard, sample load and conductivity detector. The diluent used was 50:50 acetonitrile and water with ratio of 50:50 (% v/v). The sample concentrations were fixed for the sodium in pantoprazole sodium, potassium in losartan potassium and magnesium in omeprazole magnesium as 0.2, 0.1 and 0.3 mg/mL, respectively. Finally, the single ion chromatographic method was used to determining the different percentages of counter ions in three drug substances.

Specificity: The specificity of the present method by ion chromatography is shown in Fig. 3. There was no interference among sodium, potassium and magnesium as well as lithium, ammonium and calcium. The specificity was performed by injecting system stability, blank and individual counter ions and mixed counter ions in presence of pantoprazole sodium, losartan potassium and omeprazole magnesium. Specificity results are given in Table-1.

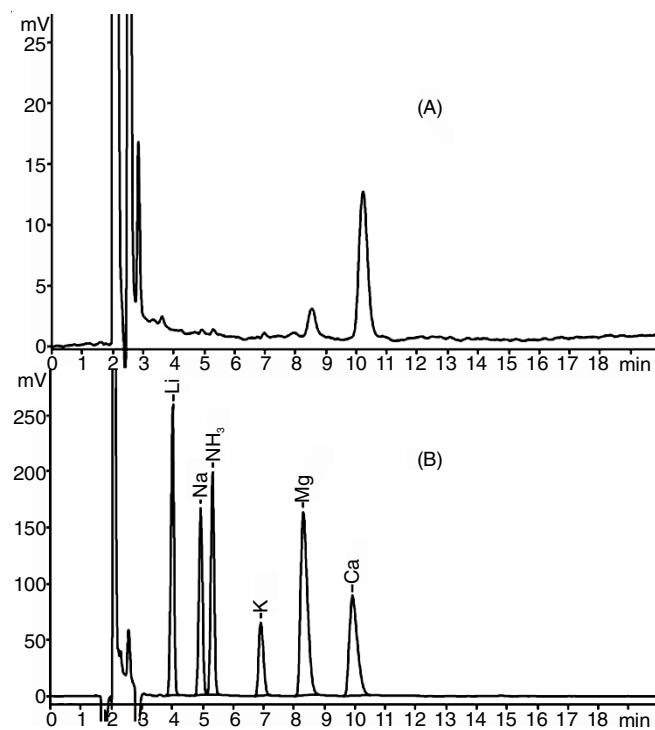


Fig. 3. Specificity chromatograms (A) Blank (B) Blend chromatogram

TABLE-1
SPECIFICITY RESULTS

S. No	Counter ions	Retention time (min)
1	Lithium	4.0
2	Sodium	4.9
3	Ammonium	5.3
4	Potassium	6.9
5	Magnesium	8.3
6	Calcium	9.9

Precision: Precision of the method was demonstrated by method precision and intermediate precision at 5.7 of sodium in pantoprazole sodium, 8.5 % of potassium in losartan potassium and 3.3 % magnesium in omeprazole magnesium. The cumulative precision at intra and inter days were performed. The % RSD values were less than 5 % for all counters, it describes the developed method was good. Precision results are given in Table-2.

Accuracy: The accuracy of method has been determined by doing the recovery studies at three different levels of counter ions at specification level. Six preparations were determined for the 100 % level *i.e.* counter ion specification level and 150 % level and three preparations were performed at 50 % level with respect to counter ion specification level. The % recovery was calculated with respect to the method precision. The % RSD for the counter ion at specification level, 50 % and 150 % were less than 10 %. The % recovery at 50, 100 and 150 % were within the range in pantoprazole sodium, losartan potassium and omeprazole magnesium. The accuracy results are give in Table-3.

TABLE-3
ACCURACY RESULTS

Concentration	Sodium	Potassium	Magnesium
Accuracy at 50 %-1	100	94	112
Accuracy at 50 %-2	93	101	115
Accuracy at 50 %-3	98	97	112
Accuracy at 100 %-1	99	93	97
Accuracy at 100 %-2	100	102	101
Accuracy at 100 %-3	100	100	98
Accuracy at 100 %-4	103	103	101
Accuracy at 100 %-5	101	97	97
Accuracy at 100 %-6	102	99	99
Accuracy at 150 %-1	93	101	96
Accuracy at 150 %-2	104	101	99
Accuracy at 150 %-3	104	101	98
Accuracy at 150 %-4	105	102	98
Accuracy at 150 %-5	105	103	100
Accuracy at 150 %-6	105	102	100

Linearity and range: The seven standards were used to prove the linearity each counter ion in respective drug substance. The ranges of 12576 ppm to 100608 ppm were selected

for sodium (1.4 % to 11.4 with respect to 5.7 %) and the correlation coefficient was 1.000. The range of 25242 to 201936 ppm was selected for potassium (2.1 % to 17 with respect to 8.5 %) and the correlation coefficient was 0.999. The range of 7898 ppm to 63180 ppm was selected for sodium (0.8 % to 6.6 with respect to 3.3 %) and the correlation coefficient was 1.000. The calibrations of sodium, potassium and magnesium are shown in Fig. 4.

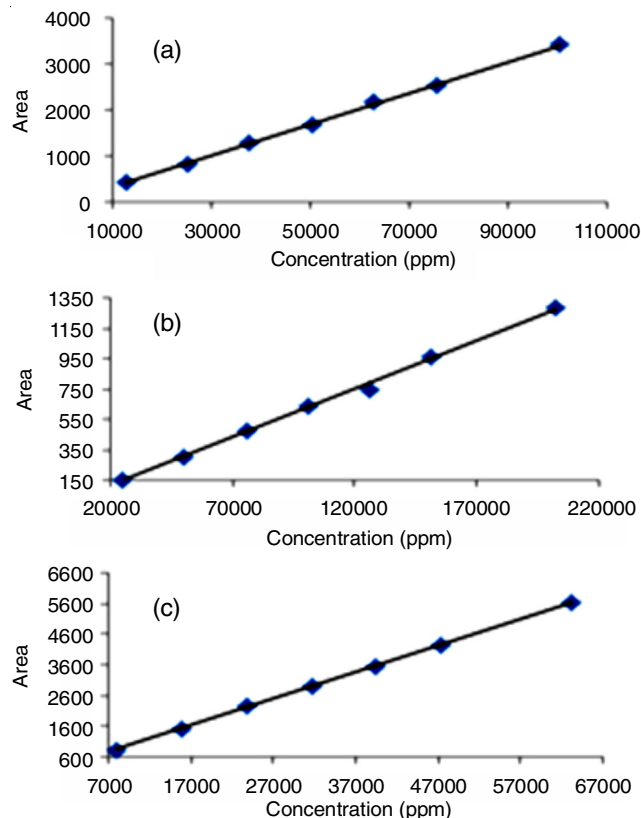


Fig. 4. Calibration curves of (a) sodium, (b) potassium and (c) magnesium

Robustness: The robustness was studied by slight variation of actual method parameters such as flow, acid strength, the present change of organic solvent. Five injections of mixed standard were injected and % RSD of three counter ions was calculated that was less than 10 % in all robustness conditions. The robustness results are given in Table-4.

Solution stability and mobile phase stability: The solution and mobile phase stability was evaluated by injecting the stored solution with intervals of 0, 12, 24, 48 and 72 h. The variation of the counter ion contents were reported which were less than 10 % with respect to initial analysis. Similarly freshly samples counter ions content were evaluated with stored mobile phase under same chromatographic conditions with intervals of 0, 12, 24, 48 and 72 h, the variation of the counter ion

TABLE-2
PRECISION RESULTS

Counter ion	Drug substance	Theoretical % of counter ion	RSD (%)			
			Method precision	Intermediate precision	150 % level precision	50 % level precision
Sodium	Pantoprazole sodium	5.7	1.6	1.6	4.8	3.7
Potassium	Losartan potassium	8.5	2.0	1.5	0.7	3.8
Magnesium	Omeprazole magnesium	3.3	1.7	2.0	1.7	1.8

TABLE-4
ROBUSTNESS RESULTS

Parameter	Actual value	Changed value	Sodium		Potassium		Magnesium	
			Std.*	VCI.	Std.*	VCI.#	Std.*	VCI.#
Flow rate	1.0 mL/min	0.9 mL/min	0.7	2.7	0.8	8.8	1.5	0.8
		1.1 mL/min	1.0	-2.6	0.7	1.4	0.7	-4.4
Acetonitrile	10 %	8 %	0.7	1.5	0.8	-1.4	1.8	-1.0
		12 %	0.7	0.3	0.7	3.3	0.6	-2.3
Nitric acid	4.0 Mm	3.6 Mm	1.0	-0.5	0.9	2.5	1.1	-2.7
		4.4 mM	1.1	0.8	0.8	4.7	1.1	-0.8

*Relative standard deviation of the counter ions (%); #Variation in counter ions (%).

TABLE-5
SOLUTION STABILITY STUDY RESULTS

Study (h)	Sodium content (%, w/w)	Variation (%)	Potassium content (%, w/w)	Variation (%)	Magnesium content (%, w/w)	Variation (%)
0 h Solution stability	5.5	–	8.1	–	3.0	–
12 h Solution stability	5.6	1.4	8.3	0.8	3.1	2.7
24 h Solution stability	5.7	3.7	8.4	3.5	3.2	5.5
48 h Solution stability	5.7	4.7	8.7	7.6	3.1	2.0
72 h Solution stability	5.9	8.0	9.1	10.4	3.3	8.9
0 h Mobile phase stability	5.6	–	8.2	–	3.1	–
12 h Mobile phase stability	5.6	1.4	8.3	1.4	3.2	3.0
24 h Mobile phase stability	5.7	1.9	8.2	0.5	3.1	1.6
48 h Mobile phase stability	5.7	2.7	8.5	5.0	3.1	0.0
72 h Mobile phase stability	5.8	4.2	8.8	7.0	3.3	5.6

contents were reported which were less than 10 % with respect to initial analysis. The solution and mobile phase stability data is given in Table-5.

Conclusion

A single counter ions convenient method was developed by ion chromatography for simultaneous determination of sodium, potassium and magnesium in pantoprazole sodium, losartan potassium and omeprazole magnesium, respectively. The best resolution was achieved by using Metrosep C₄ 250 × 4.0 × 250 mm × 5.0 µm column, 4.0 mM nitric acid and 0.1 mM dipicolinic acid mixer buffer and acetonitrile 10 %, with flow 1.0 mL and 20 micro µL load and conductivity detector. The method was validated for the precision, accuracy, linearity, range, robustness, solution and mobile phase stability. The method was specifying with remaining cat ions and it is precise, accurate, linear, robust, rugged and short runtime method for three counter ions in three drug substances, this can be used for routine analysis in quality control laboratories.

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CONFLICT OF INTEREST

All the authors have no conflicts of interest regarding the publication of the article. Dr. Reddy's has provided communication number: IPDO IPM-00574 for this research.

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