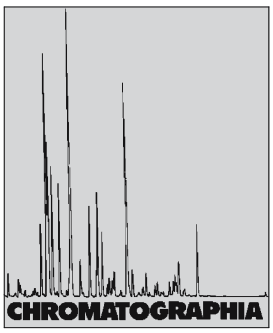
Determination of Pantoprazole, Rabeprazole, Esomeprazole, Domperidone and Itopride in Pharmaceutical Products by Reversed Phase Liquid Chromatography Using Single Mobile Phase



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Abstract

A simple, sensitive, and precise high performance liquid chromatographic method for the analysis of pantoprazole, rabeprazole, esomeprazole, domperidone and itopride, with ultraviolet detection at 210 nm, has been developed, validated, and used for the determination of compounds in commercial pharmaceutical products. The compounds were well separated on a Hypersil BDS C18 reversed-phase column by use of a mobile phase consisting of 0.05 M, 4.70 pH, potassium dihydrogen phosphate buffer - acetonitrile (720:280 *v/v*) at a flow rate of 1.0 mL min^{-1}. The linearity ranges were 400–4,000 ng mL^{-1} for pantoprazole, 200–2,000 ng mL^{-1} for rabeprazole, 400–4,000 ng mL^{-1} for esomeprazole, 300–3,000 ng mL^{-1} for domperidone and 500–5,000 ng mL^{-1} for itopride. Limits of detection (LOD) obtained were: pantoprazole 147.51 ng mL^{-1}, rabeprazole 65.65 ng mL^{-1}, esomeprazole 131.27 ng mL^{-1}, domperidone 98.33 ng mL^{-1} and itopride 162.35 ng mL^{-1}. The study showed that reversed-phase liquid chromatography is sensitive and selective for the determination of pantoprazole, rabeprazole, esomeprazole, domperidone and itopride using single mobile phase.

Keywords

Column liquid chromatography
Pharmaceutical products
Tablets
BDS column
Pantoprazole
Rabeprazole
Esomeprazole
Domperidone
Itopride

Introduction

Proton-pump inhibitors (PPIs) have emerged as the drug class of choice for treating patients with acid-related diseases, including gastro esophageal reflux disease (GERD), duodenal ulcer, and gastric ulcer. PPIs are also effective in treating patients with Barrett's esophagus and Zollinger-Ellison syndrome. These agents inhibit gastric acid secretion by targeting the gastric acid pump, H^+, K^+-adenosine triphosphatase (ATPase), in the canalicular membrane of the parietal cell [1] The regulation of acid secretion is a complex process involving many cell types, hormones, and mediators but these processes converge in a final common step involving H^+, K^+-ATPase. As a result, PPIs effectively inhibit acid secretion in a manner independent of the processes that stimulate the parietal cell [2].

Pantoprazole (PA), 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridyl) methylsulfinyl]-1*H*-benzimidazole; rabeprazole (RA), 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] methyl] sulfinyl]-1*H*-benzimidazole and esomeprazole (ES), bis(5-methoxy-2-[(*s*)-[(4-methoxy-3,5-dimethyl-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1*H*-benzimidazole-1-yl) are proton pump inhibitors [3].

Domperidone (DO), 5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1*H*-benzimidazole-1-yl) propyl]-4-piperidinyl]-1-3-dihydro-2*H*-benzimidazole-2-one is a dopamine antagonist with antiemetic property similar to metoclopramide and neuroleptic drugs. Unlike these drugs, however, domperidone does not readily cross the blood brain barrier and seldom causes extra pyramidal side effects [4, 5].

Itopride (IT), *N*-[[4-(2-dimethylamino ethoxy) phenyl] methyl]-3,4-dimethoxybenzamide, inhibits the dopamine D_2 receptor at the parasympathetic nerve

ends and thereby increases the release of acetylcholine and decreases the metabolism of acetylcholine by inhibiting the enzyme acetylcholinesterase. By maintaining higher acetylcholine levels, itopride increases the esophageal and gastrointestinal motility, accelerates gastric emptying and improves gastro duodenal co-ordination. Because of its D_2 receptor antagonistic action, it also exerts anti emetic action [6].

Many combinations of proton pump inhibitors with domperidone and itopride are available in local markets. Such a combination dosage form will be adhering to effective therapy and enhancing better patient compliance. Several techniques for example spectrophotometry, potentiometry, HPLC, LC-MS, and HPTLC have been reported in the literature for the determination of PA [7–17], RA [18–30], ES [31–34], DO [35–40] and IT [41–44] in pharmaceuticals and biological samples.

This paper describes the development and validation of RP-HPLC for assay of PA and RA in combination with DO and IT, respectively, and ES as single component in tablets by use of single mobile phase. With the developed method, only one mobile phase is sufficient for quantification of all mentioned drugs either in combination or in single dosage form as per availability of formulation. Many pharmaceutical industries manufacture their formulations of all above mentioned five drugs either in combination (depending on compability) or in single dosage form on a same day at different time intervals. Presumably, most of the pharmaceutical industries use different mobile phases for different dosage form of drugs mentioned here. But with the method that we have developed, time and cost required for changing different mobile phases could be saved, because only one mobile phase was used for all of five drugs.

Experimental

Standards and Chemicals

HPLC-grade Potassium dihydrogen phosphate (KH_2PO_4), acetonitrile (purity not less than 99.80%), methanol and triple distilled water and *o*-phosphoric acid were used as received from Merck India Ltd. (Mumbai, India). All active ingredients were obtained from Shaimil Laboratories Ltd., Baroda, India. (99.69–99.99% quality).

Solution Preparation

Stock and Working Standard Solution for PA and DO

Stock solution was prepared by weighing pantoprazole (40 mg) and domperidone (30 mg) in a 100-mL volumetric flask, dissolving in methanol and diluting to volume with the same solvent. Of these solutions, 1.0 mL was further diluted to 100 mL with mobile phase to obtain working standard solutions with pantoprazole (4,000 ng mL^{-1}) and domperidone (3,000 ng mL^{-1}). Solutions were freshly prepared before use.

Stock and Working Standard Solution for RA and IT

Stock solution was prepared by weighing rabeprazole (20 mg) and itopride (50 mg) in a 100-mL volumetric flask, dissolving in methanol and diluting to volume with the same solvent. Of these solutions, 1.0 mL was further diluted to 100 mL with mobile phase to obtain working standard solutions with rabeprazole (2,000 ng mL^{-1}) and itopride (5,000 ng mL^{-1}). Solutions were freshly prepared before use.

Stock and Working Standard Solution for ES

Stock solution was prepared by weighing esomeprazole (40 mg) in a 100-mL volumetric flask, dissolving in methanol and diluting to volume with the same solvent. Of these solutions, 1.0 mL was further diluted to 100 mL with mobile phase to obtain working standard solutions with esomeprazole (4,000 ng mL^{-1}). Solutions were freshly prepared before use.

Preparation of Internal Standard (IS) Solution

Pantoprazole and esomeprazole were used as internal standard. For simultaneous quantification of rabeprazole and itopride, pantoprazole was used as IS. Esomeprazole was used as IS for the simultaneous determination of pantoprazole and domperidone. For the determination of esomeprazole, pantoprazole was used as IS.

Internal standard solution was prepared by weighing pantoprazole (4 mg) and esomeprazole (4 mg) in a 100-mL volumetric flask, dissolving in methanol and diluting to volume with the same solvent. Of these solutions, 1.0 mL was further diluted to 100 mL with mobile phase to obtain concentration of pantoprazole (400 ng mL^{-1}) esomeprazole (400 ng mL^{-1}). Solutions were freshly prepared before use.

Preparation of Phosphate Buffer Solution

KH_2PO4 (6.8 g), previously dried for 2 h at 120 ± 5°C, was dissolved in triple distilled water, diluted to 1,000 mL with the same solvent, and adjusted to pH 4.70 ± 0.1 with 85% orthophosphoricacid.

Preparation of the Sample Solutions

PA and DO (Brand Name: PAD-30, DOM-P, PANTD, DOM PLUS)

Twenty tablets of PA and DO available as a combination dosage form were weighed and powdered. An amount of the powder, equivalent to one tablet, was weighed accurately, mixed with methanol in a 100 mL volumetric flask, sonicated for approximately 5 min, cooled to room temperature, diluted to volume with the same solvent, and filtered through nylon 0.20 µm-47 mm membrane filters to remove any insoluble matter. Filtrate (1.0 mL) was diluted to 100.0 mL with the aqueous–organic mobile phase in a volumetric flask.

RA and IT (Brand Name: RAIT, ITO-RA, RABE PLUS, RAB-I)

Twenty tablets of RA and IT taken as a combination dosage form were weighed and powdered. An amount of the powder, equivalent to one tablet, was weighed accurately, mixed with methanol in a 100 mL volumetric flask, sonicated for approximately 5 min, cooled to room temperature, diluted to volume with the same solvent, and filtered through nylon 0.20 µm–47 mm membrane filters to remove any insoluble matter. Filtrate (1.0 mL) was diluted to 100.0 mL with the aqueous–organic mobile phase in a volumetric flask.

ES (Brand Name: ESTAB, ESOM, ES-CARE, SOMPRAZ)

Twenty tablets of ES as a single dosage form were weighed and powdered. An amount of the powder, equivalent to one tablet, was weighed accurately, mixed with methanol in a 100 mL volumetric flask, sonicated for approximately 5 min, cooled to room temperature, diluted to volume with the same solvent, and filtered through nylon 0.20 μm–47 mm membrane filters to remove any insoluble matter. Filtrate (1.0 mL) was diluted to 100.0 mL with the aqueous–organic mobile phase in a volumetric flask.

Equipment

An HPLC instrument of LC-10AT VP series (Shimadzu Corporation, Switzerland) consisting of a UV-Visible detector, manual injector with 20 μL loop and Hypersil BDS C_{18} column (250 mm × 4.6 mm i.d., 5 μm particle size) was used. A Beckman Instruments (Fullerton, CA, USA) U50 pH meter was used for pH control; the instrument has previously been calibrated against standard buffer solutions of pH 1.68, 3.56, 4.01, and 6.86.

Chromatographic Condition

Chromatography was performed on a Hypersil C_{18} (2) reversed phase column (250 mm × 4.6 mm i.d., 5 μm) base deactivated silyl bonded amorphous silica. The mobile phase was potassium dihydrogen phosphate buffer-acetonitrile, 720:280 (*v*/*v*). Flow-rate was 1.0 mL min^{-1}. The column was kept at 25.0 ± 0.1 °C during the analysis; the detection wavelength was 210 nm and the injection volume was 20 μL.

Method Validation

Specificity (Selectivity)

The selectivity of the RP-HPLC method was checked by comparison of chromatograms obtained from samples and the corresponding placebo.

Linearity

Calibration curves were constructed by plotting peak areas versus concentrations of PA, RA, ES, DO and IT and the regression equations were calculated. Accurately measured standard working solution of PA, RA, ES, DO and IT (1.0, 2.0, 4.0, 6.0, 8.0, 10.0 mL) were transferred in a series of 10 mL of volumetric flask and diluted to the mark with mobile phase. Calibration curves were plotted over the concentration range of pantoprazole (400, 800, 1,600, 2,400, 3,200, 4,000 ng mL^{-1}), rabeprazole (200, 400, 800, 1,200, 1,600, 2,000 ng mL^{-1}), esomeprazole (400, 800, 1,600, 2,400, 3,200, 4,000 ng mL^{-1}), domperidone (300, 600, 1,200, 1,800, 2,400, 3,000 ng mL^{-1}), itopride (500, 1,000, 2,000, 3,000, 4,000, 5,000 ng mL^{-1}). Twenty microliter of each solution was injected under the operating chromatographic conditions described above. Each solution was injected five times. The least-squares method was used for the calculation of slope, intercept, and correlation coefficient (*r*).

Limits of Detection and Quantitation

The limits of detection (LOD) and quantitation (LOQ) were calculated in accordance with the 3.3 s m^{-1} and 10 s m^{-1}criteria, respectively, where *s* is the standard deviation of the peak area (for five replicates) for the sample and *m* is the slope of the corresponding calibration plot, determined from linearity investigation.

Accuracy

The accuracy of the RP-HPLC method was determined by calculating recoveries of pantoprazole, rabeprazole, esomeprazole, domperidone and itopride by the standard additions method. Known amounts of standard solution of PA (800, 1,600 and 2,400 ng mL^{-1}), RA (400, 800 and 1,200 ng mL^{-1}), ES (800, 1,600 and 2,400 ng mL^{-1}), DO (600, 1,200 and 1,800 ng mL^{-1}) and IT (1,000, 2,000 and 3,000 ng mL^{-1}) were added to a prequantified sample solution of PA (800 ng mL^{-1}), RA (400 ng mL^{-1}), ES (800 ng mL^{-1}), DO (600 ng mL^{-1}) and IT (1,000 ng mL^{-1}) for this method. The amount of pantoprazole, rabeprazole, esomeprazole, domperidone and itopride were estimated by applying these values to the regression equation of calibration curve.

Precision

The intra-day and inter-day precisions of the proposed methods were determined by estimating the corresponding responses five times on the same day and on three different days over a period of one week for three different concentrations of pantoprazole, rabeprazole, esomeprazole, domperidone and itopride.

Robustness

Here, small deliberate changes in the chromatographic conditions like mobile phase composition (organic modifier volume fraction, buffer pH), flow-rate and detection wavelength were done. Obtained results were compared with original chromatographic conditions.

Because the stability of standard solutions can also affect the robustness of analytical methods, the stability of the standard solutions of the drug substances used in this method was tested for one week. One portion of standard solutions was kept at room temperature and another portion was stored under refrigeration at 4°C and the content of these solutions was compared for one week with that of a freshly prepared solution.

System-Suitability Test

System-suitability tests are used to verify that the resolution and repeatability of the system were adequate for the analysis intended. The criteria used in this test were column efficiency, asymmetry of the chromatographic peak, peak resolution, and repeatability, as RSD of peak area for replicate injections. The precision of the instrument was checked by repeatedly injecting ($n = 6$) standard solution of PA (1,600 ng mL^{-1}), RA (800 ng mL^{-1}), ES (800 ng mL^{-1}), DO (1,200 ng mL^{-1}) and IT (2,000 ng mL^{-1}) for this method.

Analysis of Pharmaceutical Dosage Form (Tablets)

All tablets were purchased from a local market. The response of the tablet dosage forms was measured at 210 nm for quantification of PA, RA, ES, DO and IT by using HPLC as described above. The amount of the above mentioned drugs present in the sample solution were determined by fitting the responses into the regression equation for PA, RA, ES, DO and IT.

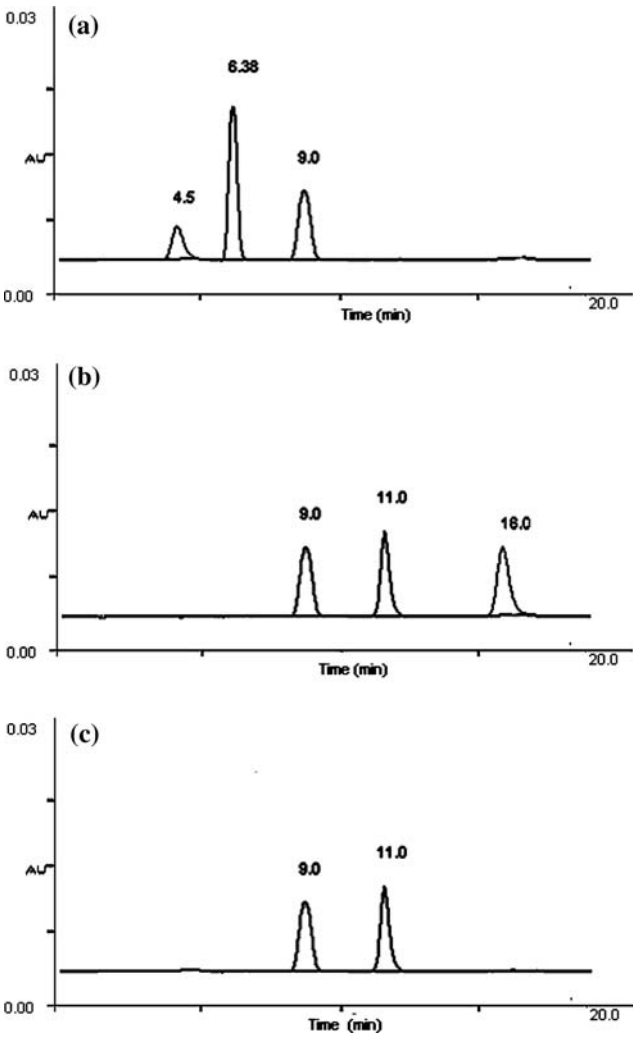

Fig. 1. **a** Chromatogram of itopride (4.5 min) and rabeprazole (6.38 min), pantoprazole (IS, 9.0 min). **b** Chromatogram of pantoprazole (9.0 min) and domperidone (16.0 min), esomeprazole (IS, 11.0 min). **c** Chromatogram of esomeprazole (11.0 min), pantoprazole (IS, 9.0 min)

Results and Discussion

To optimize the HPLC parameters, several mobile phase compositions were tried. A satisfactory separation and peak symmetry for PA, RA, ES, DO and IT were obtained with mobile phase consisting of 0.05 M, 4.70 pH, potassium dihydrogen phosphate buffer: Acetonitrile (720:280 *v*/*v*) and final pH adjusted to 6.20 ± 0.02 with acetic acid/ammonia to obtain a better reproducibility and repeatability. Quantification was achieved with UV detection at 210 nm based on the peak area. Better resolution of the peaks with clear base line separation was found (Fig. 1).

Specificity (Selectivity)

The selectivity of the RP-HPLC method was checked by comparison of chromatograms obtained from samples (tablets) and the corresponding placebo. Additives in tablets are practically insoluble in methanol or the mobile phase whereas the active constituents are freely soluble. No interference from additives of the tablets was obtained.

Linearity

The linear correlation between the peak area and compound was checked for each component. Data for six solutions of different concentration of PA (400, 800, 1,600, 2,400, 3,200, 4,000 ng mL^{-1}), RA (200, 400, 800, 1,200, 1,600, 2,000 ng mL^{-1}), ES (400, 800, 1,600, 2,400, 3,200, 4,000 ng mL^{-1}), DO (300, 600, 1,200, 1,800, 2,400, 3,000 ng mL^{-1}), IT (500, 1,000, 2,000, 3,000, 4,000, 5,000 ng mL^{-1}) were collected and analyzed. The least squares method was used for calculation of slope, intercept and correlation coefficient (*r*). For all the compounds the correlation between the peak area and substance concentration were described by linear regression equations with high values of correlation coefficient *r*. All results are listed in Tables 1 and 2.

Limit of Detection and Limit of Quantification

LOD for PA, RA, ES, DO and IT were found to be 147.51 ng mL^{-1}, 65.65 ng mL^{-1}, 131.27 ng mL^{-1}, 98.33 ng mL^{-1} and 162.35 ng mL^{-1}, respectively by this method.

LOQ for PA, RA, ES, DO and IT were found to be 399.63 ng mL^{-1}, 198.69 ng mL^{-1}, 397.79 ng mL^{-1}, 297.98 ng mL^{-1} and 498.32 ng mL^{-1}, respectively by this method (Table 2).

Accuracy

The recovery experiments were carried out by the standard addition method. The percent age of the recoveries obtained were 100.05 ± 0.80, 99.51 ± 0.23, 99.40 ± 0.47, 99.48 ± 29 and 99.59 ± 0.57 for PA, RA, ES, DO and IT, respectively (Table 2). The recovery of the method was good.

Precision

The low % RSD values of inter-day (0.19 – 1.719) and intra-day (0.74 – 1.82) implied that the reproducibility of the proposed method was good (Table 2).

Robustness

The method was found to be robust, although small deliberate changes in method conditions did have a negligible effect on the chromatographic behavior of the solutes. The results indicate that changing the pH (±0.05) and mobile phase flow-rate had no large effect on the chromatographic behavior of pantoprazole, rabeprazole, esomeprazole, domperidone and itopride. Even a small change of pH did not cause a notable change in the retention time of the used

Table 1. Results from regression analysis of the calibration curves

Parameters	Pantoprazole	Rabeprazole	Esomeprazole	Domperidone	Itopride
Intercept	−16,474	7,124.63	16,557.67	19,850	5,786
Slope	334.34	217.59	182.54	246.11	190.17
Correlation coefficient	0.997	0.993	0.994	0.996	0.999

Table 2. Summary of validation parameters for the proposed method

Parameters	Pantoprazole	Rabeprazole	Esomeprazole	Domperidone	Itopride
Linearity (ng mL^{-1})	400–4,000	200–2,000	400–4,000	300–3,000	500–5,000
LOD (ng mL^{-1})	147.51	65.657	131.27	98.33	162.35
LOQ (ng mL^{-1})	399.63	198.69	397.79	297.98	498.32
Accuracy (%) precision (% RSD)	99.91–100.20	99.13–99.89	98.96–99.85	99.01–99.95	98.86–99.32
Interaday ($n = 5$)	0.74–1.73	0.32–0.42	0.43–0.65	0.49–0.92	0.84–1.82
Interday ($n = 7$)	0.63–1.71	0.52–1.51	0.61–1.67	0.19–0.80	1.39–1.58
Repeatability (% RSD)	0.538	0.278	0.380	0.155	1.038

LOD limit of detection
LOQ limit of quantification
RSD relative standard deviation
n number of determination

Table 3. Summary of system suitability parameters

Parameters	Pantoprazole	Rabeprazole	Esomeprazole	Domperidone	Itopride
Retention Time (min) ± RSD	9.0 ± 0.01	6.38 ± 0.02	11.0 ± 0.01	16.00 ± 0.02	4.5 ± 0.01
Theoretical plates ± RSD	8,860 ± 0.08	8,550 ± 0.09	7,540 ± 0.06	8,800 ± 0.1	7,680 ± 0.09
Tailing factor ± SD	1.06 ± 0.05	1.15 ± 0.02	1.09 ± 0.01	1.08 ± 0.03	1.02 ± 0.01

RSD relative standard deviation

Table 4. Results from assay of tablets by use of RP HPLC method

Assay mean ± SD				
Combine dosage form 1		Combine dosage form 2		Single dosage form
Pantoprazole	Domperidone	Rabeprazole	Itopride	Esomeprazole
Sample 1		Sample 5		Sample 9
99.75 ± 0.275	100.31 ± 0.255	100.55 ± 0.265	99.97 ± 0.245	100.52 ± 0.154
Sample 2		Sample 6		Sample 10
100.01 ± 0.246	100.64 ± 0.243	99.47 ± 0.160	99.86 ± 0.213	100.22 ± 0.103
Sample 3		Sample 7		Sample 11
99.91 ± 0.206	100.10 ± 0.299	99.75 ± 0.311	99.98 ± 0.125	99.92 ± 0.199
Sample 4		Sample 8		Sample 12
99.88 ± 0.288	99.94 ± 0.213	100.37 ± 0.426	100.01 ± 0.202	100.15 ± 0.159

Samples 1–4: four different brands of pantoprazole and domperidone, samples 5–8: four different brands for rabeprazole and itopride, samples 9–12: four different brands for esomeprazole
SD standard deviation

drugs for this method. A minor increase or decrease of the in flow-rate (±0.010) did also not cause any change in the tailing of the peak of each drug. Alteration of the detection wavelength (±5 nm) caused no variation of peak areas and did not affect the chromatographic behavior of pantoprazole, rabeprazole, esomeprazole, domperidone and itopride of the method.

The stability of standard solutions may also affect the robustness of analytical methods. The stability of the standard solutions of the drug substances used in this method was tested for one week. One portion of standard solutions was kept at room temperature and another portion was stored under refrigeration at 4°C and the content of these solutions was compared regularly with that of a freshly prepared solution. No changes in drug concentrations were observed for the solutions stored under refrigeration.

System-Suitability Test

The percentage of relative standard deviation (% RSD) for PA, RA, ES, DO and IT were found to be 0.53, 0.27, 0.38, 0.15 and 1.03, respectively using this method (Table 2, 3). All the results were within the acceptable range.

Assay of The Tablet Dosage Form

The proposed validated method was successfully applied to determine PA, RA, ES, DO and IT in pharmaceutical products (sample 1–12). The results obtained for PA, RA, ES, DO and IT were comparable with the corresponding labeled amounts (Table 4).

Conclusion

A new, simple, sensitive, accurate, reproducible, and precise RP HPLC method for assaying pantoprazole, rabeprazole, esomeprazole, domperidone and itopride in tablets has been developed and validated. The proposed method uses a mobile phase consisting of 0.05M, pH 4.70, potassium dihydrogen phosphate buffer solution and acetonitrile (720:280 (*v*/*v*)) for the separation of pantoprazole, rabeprazole, esomeprazole**,** domperidone and itopride.

This method uses a common mobile phase for the separation of five different drugs in combination and in single dosage form. Analytical control for in-process quality control (IPQC) may demand the change of the mobile phase for different drugs mentioned here. Since we only required to use one mobile phase, this proposed method can save labor, cost and time of analysis for changing mobile phases.

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