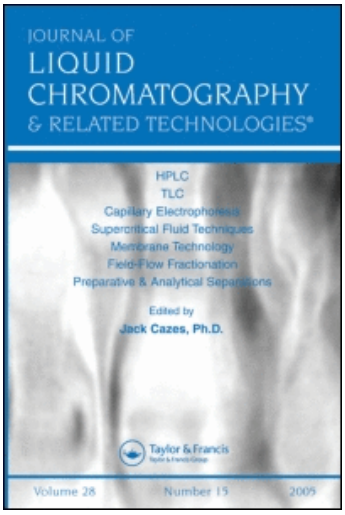

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Simultaneous Determination of Omeprazole and Domperidone in Capsules by RP-HPLC and Densitometric HPTLC

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Simultaneous Determination of Omeprazole and Domperidone in Capsules by RP-HPLC and Densitometric HPTLC

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Abstract: A rapid, simple, and sensitive HPLC and a densitometric HPTLC method for the determination of omeprazole and domperidone in capsule formulations were developed and validated. For HPLC, the separation of components was achieved on a Phenomenex Rp-C_{18} column. Isocratic elution with a mobile phase consisting of 0.01 M pH 6.5, ammonium acetate buffer: methanol:acetonitrile (40:30:30 v/v, pH 7.44 $\pm$ 0.02), at a flow rate 1.0 mL/min was employed. Rabeprazole was used as the internal standard. In densitometric HPTLC, separation was achieved on aluminum sheets of silica gel 60F_{254} using ethyl acetate:methanol:benzene (40:20:40 v/v) as mobile phase. Linear concentration range of HPLC and HPTLC methods were between 400–2000 ng/mL and 120–360 ng/spot for both the drugs, respectively. In HPLC, the detection limit was 131.27 ng/mL for omeprazole and 131.20 ng/mL for domperidone, the mean analytical recovery in determination of omeprazole and domperidone capsules was 99.14 $\pm$ 1.81 for omeprazole and 99.63 $\pm$ 1.68 for domperidone. Whereas, the detection limit was 40.83 ng/spot for omeprazole and 40.53 ng/spot for domperidone, the mean analytical recovery in determination of omeprazole and domperidone capsules was 99.51 $\pm$ 0.91 and 99.48 $\pm$ 1.15, respectively, in HPTLC. The components were detected by UV detection at 295 nm. Thus, the proposed method is applicable for routine determination of omeprazole and domperidone in pharmaceutical formulations.

Keywords: Omeprazole, Domperidone, Rabeprazole, RP-HPLC, HPTLC, Capsules

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INTRODUCTION

Omeprazole,5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-yridinyl)methyl]sulfinyl]-1H-benzimidazole, is a selective and irreversible proton pump inhibitor used in medicine as an antiulcerative agent.[1] The final step in the pathway for acid secretion from the parietal cell into the gastric lumen is the so called 'proton pump'. The proton pump is an active transport system that is powered by the enzyme H^+/K^+-ATPase, which catalyzes the exchange of intra-cellular hydrogen ions for extra cellular potassium ions. The inhibition of the proton pump will prevent acid secretion from the parietal cell.[2]

Different analytical methods for determination of omeprazole in biological fluids and in pharmaceutical formulations have been developed by using high performance liquid chromatography (HPLC) with coulometric detection, spectrophotometry, voltammetry, and polarography. It has also been determined in the presence of its photo degradation products by derivative spectrophotometry and complex formation.[3–22]

Chemically, domperidone is 5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1H-benzimidazole-1-yl) propyl]-4-piperidinyl]-1-3-dihydro-2H-benzimidazole-2-one. It is a peripheral dopamine -2 receptor antagonist. It is a unique gastrokinetic and antiemetic drug.[23] As far as domperidone is concerned, many reports are available for its estimation in pure powder and formulation using HPLC, spectrophotometry, HPTLC in combination with pantoprazole, cinnarazine, and ranitidine.[24–30]

Since pharmacopoeias do not describe a suitable method for the concurrent determination of omeprazole and domperidone in pharmaceutical formulations, in the present work we developed rapid, accurate HPLC and HPTLC methods for the simultaneous determination of omeprazole and domperidone in capsules as an alternative method. Apart from this, it can be used for assays of omeprazole and domperidone in biological fluids or in pharmacokinetic investigations.

EXPERIMENTAL

Apparatus

A Shimadzu HPLC instrument (LC-10AT vp) equipped with UV-Visible detector, manual injector with 20 μLloop, and Phenomenex C_{18} column (250 mm × 4.6 mm i.d., 5 μm particle size) was used. A Camag HPTLC with Linomat V auto sprayer, Camag Scanner-III, Camag flat bottom and twin trough developing chamber, and UV cabinet with dual wavelength UV lamp was used. HPTLC plates used were of silica gel with fluorescent indicator 254 nm, layer thickness (0.2 mm) 20 × 10 cm aluminum (E-Merck-KgaA).

Reagents and Materials

Torrent Pharmaceutical, Ahmedabad, India, kindly gifted omeprazole, rabeprazole, and domperidone pure powder with 99.94%, 99.82%, and 99.98% purity, respectively. HPLC grade methanol and acetonitrile were purchased from S.D. Fine Chemical, Ahmedabad, India. The water for HPLC was prepared by triple glass distillation and filtered through nylon 0.45 μm–47 mm membrane filter (Gelman laboratory, Mumbai, India). Ethyl acetate, ammonium acetate, benzene, acetic acid, and ammonia were procured from S.D. Fine Chemical, Ahmedabad, India and were of analytical grade.

Chromatographic Conditions

HPLC Method

A Phenomenex C_{18}[2] column (250 mm × 4.6 mm i.d., 5 μm) was used at ambient temperature. The mobile phase comprised of 0.01 M, pH 6.5 ammonium acetate buffer: methanol:acetonitrile (40:30:30 v/v/v), and final pH adjusted to 7.44 ± 0.02 with acetic acid/ammonia was pumped at a flow rate of 1 mL/min. The mobile phase was filtered through nylon 0.45 μm–47 mm membrane filters and was degassed before use. The elution was monitored at 295 nm. The injection volume was 20 μL.

HPTLC Method

Solutions of the omeprazole and domperidone were applied to silica gel $60F_{254}$ TLC plates (20 × 10 cm) by means of a Linomat V automatic spotter equipped with a 100 μL syringe. The plate was developed in a developing chamber previously saturated for 30 minutes with mobile phase; ethyl acetate:methanol:benzene (40:20:40 v/v/v) to 8 cm. The spots were scanned with a Camag Scanner III at 295 nm. Chromatographic estimations were performed under the following conditions: stationary phase, precoated silica gel $60F_{256}$ aluminium sheets (20 × 10 cm, prewashed with methanol and dried in air), chamber saturation time 30 min, temperature 25 ± 2°C, and slit dimensions 4 × 0.1 mm.

The following spotting parameters were used: band width 4 mm, space between two bands 4 mm, and spraying rate 10 μL.

Preparation of Omeprazole and Domperidone Standard Stock Solutions

HPLC Method

Accurately weighed omeprazole and domperidone (10 mg) were transferred to a 100 mL volumetric flask, dissolved in and diluted to the mark with methanol,

to obtain a standard solution having a concentration of omeprazole and domperidone (100 μg/mL). One mL of this solution was further diluted to 50 mL with mobile phase to obtain a working standard solution with omeprazole and domperidone (2 μg/mL) for the HPLC method. To each solution rabeprazole sodium was added (800 ng/mL) so that its concentration was always the same.

HPTLC Method

Accurately weighed omeprazole and domperidone (10 mg) were transferred to a 100 mL volumetric flask, dissolved in and diluted to the mark with methanol, to obtain a standard solution having a concentration of omeprazole and domperidone (100 μg/mL) for the HPTLC method.

Preparation of Sample Solutions

Powder (pellets) of each of 10 capsules (2 brands) were weighed and analyzed as follows. A mass of pellets (powder) equivalent to the powder of one capsule was weighed and transferred in a 100 mL volumetric flask and methanol (80 mL) was added. It was sonicated for 15 minutes and final volume was made to the mark with methanol to get a solution with omeprazole and domperidone (100 μg/mL). The mixture was then filtered through a nylon 0.20 μm–47 mm membrane filter.

Method Validation

Specificity (Selectivity)

The selectivity of the RP HPLC and HPTLC methods were checked by comparison of chromatograms obtained from samples and the corresponding placebo. Additives in capsules are sparingly soluble in methanol or the mobile phase, whereas the active constituents are freely soluble.

Linearity

HPLC Method

Calibration curves were constructed by plotting peak areas versus concentrations of omeprazole and domperidone and the regression equations were calculated. A calibration curve was plotted over a concentration range 400–2000 ng/mL for both drugs. Accurately measured standard working solutions of omeprazole and domperidone (0.5, 1.0, 2.0, 3.0, 4.0, 5.0 mL) were transferred in a series of 10 mL volumetric flasks and diluted to the

mark with mobile phase. Of each solution, 20 μL was injected under operating chromatographic conditions described above.

HPTLC Method

Analysis was performed on a 20 × 10 cm HPTLC silica gel $60F_{254}$ aluminum plate. Calibration curves were plotted over a concentration range 120–360 ng/spot for both the drugs.

For the calibration curves, accurately prepared standard solutions of omeprazole and domperidone (1.2, 1.6, 2.0, 2.4, 2.8, 3.2, 3.6 μL) were applied to the plate. The plate was developed in a developing chamber previously saturated with the mobile phase for 30 minutes. After development, the plate was dried in air and standard zones were quantified by linear scanning at 295 nm by a Camag TLC scanner-III with a deuterium source. The calibration curves were constructed by plotting peak areas versus concentrations with the help of win-CATS (one software to manage all TLC steps). Each reading was the average of three determinations.

Accuracy (% Recovery)

The accuracy of the methods was determined by calculating recoveries of omeprazole and domperidone by the standard additions method. Known amounts (400, 800, 1200 ng/mL) of standard solution of omeprazole and domperidone for the HPLC method, while 120, 160, 200 ng/spot for both the drugs for the HPTLC method were added to a prequantified sample solution (400 ng/mL and 120 ng/spot) of capsule dosage forms for the HPLC method and HPTLC method. The amounts of omeprazole and domperidone were estimated by applying these values to the regression equation of the calibration curve.

Precision

Method Precision (Repeatability)

The precision of the instruments was checked by repeatedly (n = 6) injecting 1200 ng/mL standard solutions of omeprazole and domperidone for the HPLC method and by repeated scanning (n = 6) of the same spot of omeprazole and domperidone with concentration of 160 ng/spot, without changing the position of plate for HPTLC method.

Intermediate Precision (Reproducibility)

The intra-day and inter-day precisions of the proposed methods were determined by estimating the corresponding responses 3 times on the same day and on 3 different days over a period of 1 week, for 3 different concentrations of 400, 1600, 2000 ng/mL for omeprazole and domperidone for the HPLC method and 160, 240, 320 ng/spot concentration of omeprazole and

domperidone for the HPTLC method. The results are reported in terms of relative standard deviation.

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 these methods was tested over a long period of time. One portion of a standard solution was kept at room temperature and another portion was stored under refrigeration at approximately 4°C, and the content of these solutions was regularly compared with that of a freshly prepared solution.

Limit of Detection and Limit of Quantification

The limit of detection and the limit of quantification of the drug was calculated using the following equations as per ICH guidelines.[31]

$$\text{LOD} = 3.3 \times \sigma/\text{S}$$
$$\text{LOQ} = 10 \times \sigma/\text{S}$$

Where $\sigma =$ the standard deviation of the response, S = the standard deviation of y-intercept of regression lines.

Analysis of Omeprazole and Domperidone in Combined Capsule Dosage Form

Capsules containing omeprazole and domperidone (10 mg) of the following two brands, Alkem lab ltd., Mumbai, India and Shaimil laboratory, Baroda, India were purchased from the local market. The response of capsule dosage forms were measured at 295 nm for quantification of omeprazole and domperidone, respectively, by using HPLC and HPTLC instruments as described above. The amount of omeprazole and domperidone present in sample solutions were determined by fitting the responses into the regression equation for omeprazole and domperidone.

RESULTS AND DISCUSSION

HPLC Method

To optimize the HPLC parameters, several mobile phase compositions were tried. A satisfactory separation and peak symmetry for omeprazole and domperidone were obtained with a mobile phase consisting of 0.01 M 6.5 pH ammonium acetate buffer: methanol:acetonitrile (40:30:30 v/v) and final pH adjusted to 7.44 $\pm$ 0.02 with acetic acid/ammonia to get better reproducibility and repeatability. Quantification was achieved with UV detection at

295 nm based on peak area. The retention times were 5.99, 6.82, 8.51 for omeprazole, rabeprazole (IS) and domperidone, respectively. A good resolution of the peaks with clear base line separation was found (Fig. 1).

HPTLC Method

Several mobile phases were tried to accomplish good separation of omeprazole and domperidone. Using this mobile phase, ethyl acetate:methanol:benzene (40:20:40 v/v) and 20 × 10 cm HPTLC silica gel $60F_{254}$ aluminum plates, better separation was attained where R_f values were to be 0.77 for omeprazole and 0.61 for domperidone. A wavelength of 295 nm was used for the quantification of the drugs. Good resolution of the peaks with clear base line separation was found (Fig. 2).

Validation of the Proposed Methods

Specificity (Selectivity)

The selectivity of the RP, HPLC, and HPTLC methods was checked by comparison of chromatograms obtained from samples and the corresponding placebo. No interference from additives was obtained.

Linearity

Linear correlation was obtained between peak areas and concentrations of omeprazole and domperidone in range of 400–2000 ng/mL for HPLC and

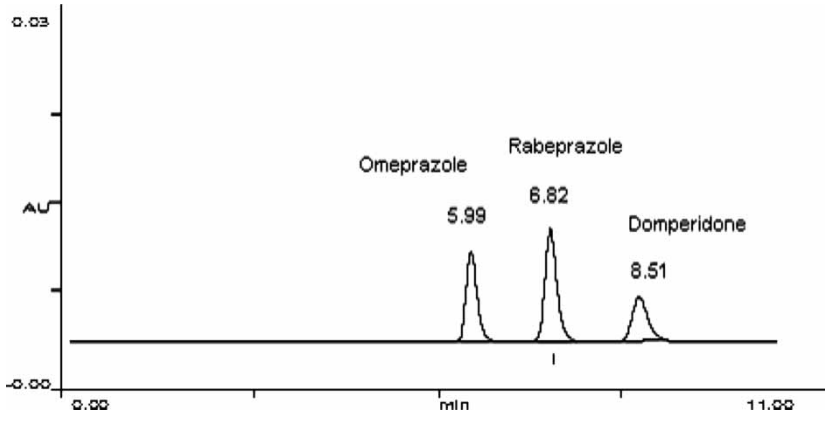

Figure 1. Chromatogram of omeprazole and domperidone by HPLC. Rabeprazole was added as IS.

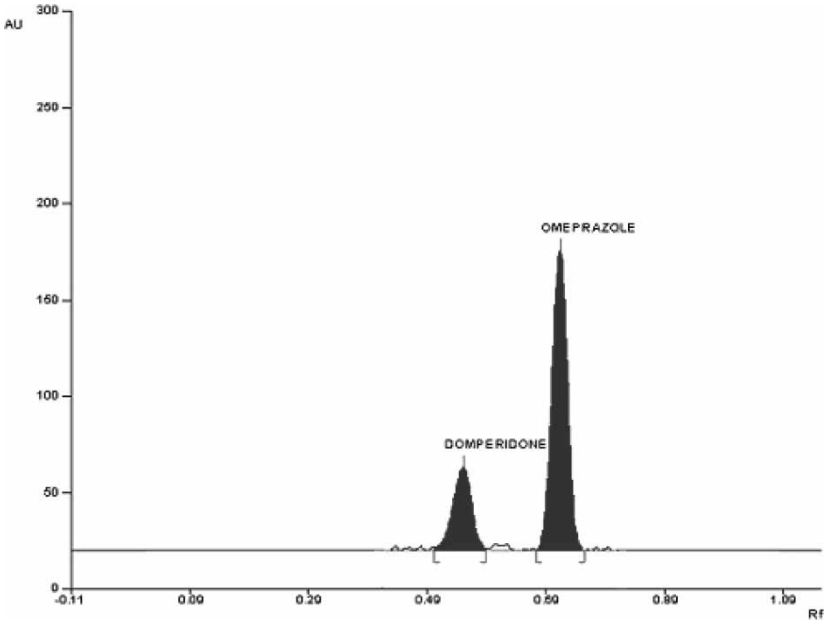

Figure 2. Chromatogram of omeprazole and domperidone by HPTLC.

120–360 ng/spot for HPTLC. The linearity of the calibration graphs was validated by the high value of correlation coefficients of the regression (Table 1).

Accuracy

The recovery experiments were carried out by a standard addition method. The percent recoveries obtained were 99.14 $\pm$ 1.81 and 99.63 $\pm$ 1.68 for omeprazole and domperidone, respectively by HPLC and 99.51 $\pm$ 0.91 and 99.48 $\pm$ 1.15 for omeprazole and domperidone, respectively, by HPTLC (Table 2). The low value of SD indicates that both the methods are accurate.

Precision

Method Precision

The percentage relative standard deviation (% RSD) for omeprazole and domperidone in combined formulation was found to be 0.3818 and 1.1788, respectively, using the HPLC method, while 1.0235 and 1.5522, respectively, by HPTLC (Table 2). The lower values of % RSD indicate the proposed methods are repeatable.

Table 1. Regression analysis of the calibration curves for omeprazole and domperidone for the proposed HPLC and HPTLC methods

	HPLC method		HPTLC method	
Parameter	Omeprazole	Domperidone	Omeprazole	Domperidone
Concentration range	400–2000 ng/mL	400–2000 ng/mL	120–360 ng/spot	120–360 ng/spot
Slope	246.11	182.74	14.61	4.97
Standard deviation of slope	2.0888	0.1078	0.0519	0.2007
Intercept	−19850	16567.67	285.45	14.61
Standard deviation of intercept	31.79	20.84	11.40	1.23
Correlation coefficient	0.9956	0.9946	0.9966	0.9998

Table 2. Summary of validation parameters for the proposed HPLC and HPTLC methods

	HPLC method		HPTLC method	
Parameter	Omeprazole	Domperidone	Omeprazole	Domperidone
LOD*	131.27 ng/mL	131.20 ng/mL	40.83 ng/spot	40.53 ng/spot
LOQ**	397.79 ng/mL	397.60 ng/mL	123.73 ng/spot	122.84 ng/spot
Accuracy (%)	97.12–100.63	98.57–101.58	98.88–100.56	98.34–100.65
Repeatability (RSD***, n = 6)	0.3818	1.1788	1.0235	1.5522
Precision (RSD)				
Interday (n**** = 3)	0.6397–1.7194	0.1989–0.8042	1.0688–1.5103	1.6685–1.1435
Intraday (n = 3)	0.1851–0.4312	0.1513–0.4575	1.1885–1.5295	1.2954–1.7956

Where, LOD* = Limit of detection, LOQ** = Limit of quantification, RSD*** = Relative standard deviation, n**** = Number of determination.

Intermediate Precision

For HPLC, the low % RSD values of inter-day was found to be 0.693–1.719 and 0.198–0.804, while % RSD values of intra-day was found to be 0.1851–0.4312 and 0.199–0.826 for omeprazole and domperidone, respectively.

For the HPTLC method, the % RSD values of inter-day was found to be 1.0688–1.5103 and 0.6685–1.1435, while % RSD values of intra-day was found to be 1.1885–1.5295 and 1.2954–1.7956 for omeprazole and domperidone, respectively. The low % RSD values of intra-day and inter-day variations reveal that the proposed methods are robust (Table 2).

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 these methods were tested over a long period of time. One portion of a standard solution was kept at room temperature and the other portion was stored under refrigeration at approximately 4°C, and the content of these solutions was regularly compared with that of a freshly prepared solution. No changes in drug concentrations were observed for solutions stored under refrigeration. But, it is recommended that the standard and sample solutions must, therefore, be freshly prepared in amber colored flasks to protect from light for both of the methods.

Limit of Detection and Limit of Quantification

The limit of detection and the limit of quantification of the drugs were calculated as in the text. LODs for omeprazole and domperidone were found to be 131.27 ng/mL and 131.20 ng/mL, respectively, by HPLC and 40.83 ng/spot and 40.53 ng/spot, respectively, by HPTLC. LOQs for omeprazole and domperidone were found to be 397.79 ng/mL and 397.65 ng/mL, respectively, by HPLC and 119.73 ng/spot and 118.69 ng/spot, respectively, by HPTLC (Table 2). These data show that both the methods are sensitive for the determination of omeprazole and domperidone.

Assay of the Capsule Dosage Form (Omeprazole 10 mg and Domperidone 10 mg per Capsule)

The proposed validated methods were successfully applied to determine omeprazole and domperidone in their combined capsule dosage form (Capsule A and B). The results obtained for omeprazole and domperidone was comparable with the corresponding labeled amounts (Table 3).

Table 3. Assay results of combined dosage form using the proposed HPLC and HPTLC method

	Omeprazole ± SD* (n** = 5)		Domperidone ± SD* (n** = 5)	
Formulation	HPLC	HPTLC	HPLC	HPTLC
A	101.09 ± 0.34	99.52 ± 0.34	100.22 ± 0.19	100.18 ± 1.18
B	100.32 ± 1.09	99.30 ± 0.57	99.67 ± 0.34	100.97 ± 2.30

Where, SD* = Standard deviation. n** = Number of determination.

CONCLUSION

The results of the analysis of pharmaceutical dosage forms by the proposed methods are highly reproducible, reliable, and are in good agreement with the label claims of the drug. The additives usually present in the pharmaceutical formulations of the assayed samples did not interfere with omeprazole and domperidone.

It may be said that the proposed methods are precise, sensitive, and accurate, so that these can be used as standard pharmacopoeial methods for the simultaneous determination of omeprazole and domperidone in capsules using the HPLC and HPTLC systems. The advantages of the proposed methods involve a simple procedure for sample preparation and relatively short time of analysis. Apart from this, it can be used for assays of omeprazole and domperidone in biological fluids or in pharmacokinetic investigations.

Comparison of the Proposed Methods

The assay results for omeprazole and domperidone in their combined dosage forms obtained using HPLC and HPTLC methods were compared by applying the paired t-test. The calculated t value 0.43 for omeprazole and 0.19 for domperidone is less than the tabulated t-value (4.60) at 95% confidence interval. Therefore, there is no significant difference in the content of omeprazole and domperidone by the HPLC and HPTLC methods. Here, comparison was also done with an already established RP HPLC method of omeprazole and domperidone for analysis of such drug components simultaneously.[27] The results from assays of the drugs were compared; statistical analysis using the Student t-test and the variance ratio F test showed there was significant difference between the results; this proposed method had a significant difference between the accuracy and precision of available RP HPLC. Comparison revealed that the proposed HPLC method was sensitive and selective. The calculated t and F values were less than the theoretical values at 95% confidence level.

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