ACTA CHROMATOGRAPHICA, NO. 18, 2007

DEVELOPMENT AND VALIDATION OF A REVERSED-PHASE HPLC METHOD FOR SIMULTANEOUS DETERMINATION OF DOMPERIDONE AND PANTOPRAZOLE IN PHARMACEUTICAL DOSAGE FORMS

T. Sivakumar[*], *R. Manavalan*, and *K. Valliappan*

Department of Pharmacy, Annamalai University, Annamalai Nagar, Tamil Nadu-608 002, India

SUMMARY

A simple reversed-phase high-performance liquid chromatographic (RP-HPLC) method has been developed and validated for simultaneous determination of domperidone and pantoprazole in capsules. The compounds were separated on an ODS analytical column with a mixture of methanol, acetonitrile, and triethylamine solution (10 mM, pH 7.0 ± 0.05 adjusted with 85% phosphoric acid) in the ratio 20:33:47 (*v*/*v*) as mobile phase at a flow rate of 1.0 mL min^{-1}. UV detection was performed at 285 nm. The method was validated for accuracy, precision, specificity, linearity, and sensitivity. The developed and validated method was successfully used for quantitative analysis of Pantop-D capsules. Total chromatographic analysis time per sample was approximately 10 min with pantoprazole, acetophenone (internal standard), and domperidone eluting with retention times of 4.34, 5.52, and 9.46 min, respectively. Validation studies revealed the method is specific, rapid, reliable, and reproducible. Calibration plots were linear over the concentration ranges 0.5–5 μg mL^{-1} and 1–10 μg mL^{-1} for domperidone and pantoprazole, respectively. The LODs were 15.3 and 3.0 ng mL^{-1} and the LOQs were 51.0 and 10.1 ng mL^{-1} for domperidone and pantoprazole, respectively. The high recovery and low relative standard deviation confirm the suitability of the method for determination of domperidone and pantoprazole in capsules.

INTRODUCTION

Domperidone (DP), 5-chloro-1-[1-[3-(2,3-dihydro-2-oxo-1*H*-benzimidazol-1-yl)propyl]-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one

(Fig. 1), is a potent dopamine antagonist used for treatment of nausea and vomiting. DP does not cross the blood–brain barrier and therefore has fewer adverse CNS effects than other dopamine antagonists [1,2]. DP has been determined in human plasma [3], human serum and human milk [4], and rat plasma [5], has been evaluated in coevaporates by HPLC [6], and has been determined, with cinnarizine, in tablets, by HPLC [7].

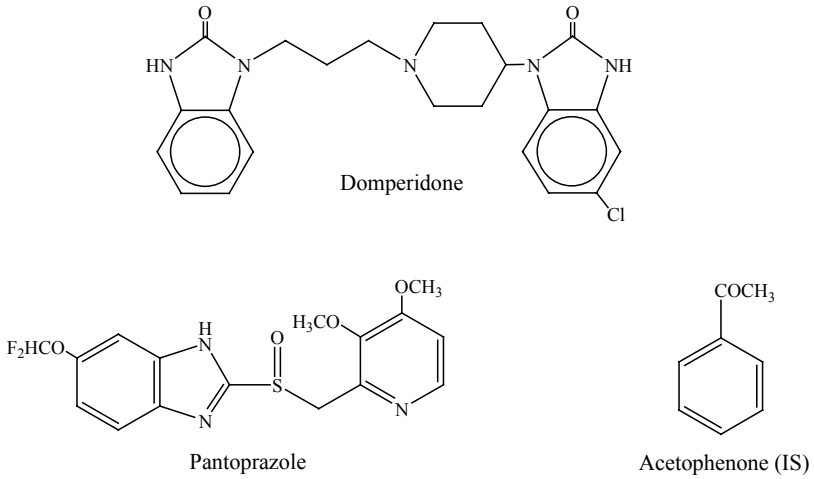

Fig. 1

The chemical structures of the analytes and the internal standard (IS).

Pantoprazole (PP), 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulphinyl]-1*H*-benzimidazole (Fig. 1), is a selective and long-acting proton-pump inhibitor used for treatment of acid-related gastrointestinal disorders. According to the literature HPLC has been used for determination of PP in serum and plasma [8] and in tablet dosage forms [9], and for enantioselective separation of omeprazole and three analogues on different chiral stationary phases [10]. Chiral resolution of PP and related sulphoxides has been performed by capillary zone electrophoresis using bovine serum albumin as the chiral selector [11]. Separation of the enantiomers of PP by multidimensional HPLC [12] has also been reported.

In recent years pharmaceutical preparations containing both these drugs have been available commercially. Although, many methods for estimation of DP and PP individually have been reported in the literature, no single method is available for their simultaneous determination. Because use of this preparation is increasing rapidly, however, it is essential to

develop a suitable analytical method for simultaneous estimation of DP and PP in pharmaceutical preparations. Because HPLC methods have been widely used for routine quality-control assessment of drugs, because of their sensitivity, repeatability, and specificity, we have developed a simple and specific RP-HPLC method for simultaneous determination of DP and PP in pharmaceutical dosage forms. Because analytical methods must be validated before use by the pharmaceutical industry, the proposed HPLC–UV method was validated in accordance with International Conference on Harmonization (ICH) guidelines [13,14], by assessing its selectivity, linearity, accuracy, precision, and limits of detection and quantitation.

EXPERIMENTAL

Materials

Domperidone and pantoprazole were kind gifts from Madras Pharmaceuticals, Chennai, India. Acetophenone (internal standard, IS) and triethylamine (TEA) were purchased from Fluka (Buchs, Switzerland). Commercially available Pantop-D capsules (containing 10 mg DP and 20 mg PP) were obtained from Aristo Pharmaceuticals (Mumbai, India). Acetonitrile (ACN) and methanol (MeOH) of HPLC grade and other reagents of analytical-reagent grade were from SD Fine Chemicals (Mumbai, India). HPLC-grade water was prepared by use of a Millipore (Bangalore, India) Milli-Q Academic water purifier.

Chromatographic System and Conditions

Analysis was performed with a Shimadzu (Japan) chromatograph equipped with an LC-10 AD *vp* solvent-delivery module, an SPD-10A UV–visible detector, and a Rheodyne model 7125 injector valve with 20-µL sample loop. DP, PP, and the IS were separated on a Phenomenex ODS analytical column (150 mm × 4.6 mm i.d., 5-µm particles) under reversed-phase partition chromatographic conditions. The mobile phase was a mixture of MeOH, ACN, and TEA solution (10 mM, pH 7.0 ± 0.05 adjusted with 85% phosphoric acid) in the ratio 20:33:47 (*v*/*v*). The flow rate was 1.0 mL min^{-1} and the analytes and the internal standard were monitored at 285 nm. The equipment was controlled by a PC workstation with Shimadzu LC Solution, Release 1.11SP1, chromatography software installed. The system was used in an air-conditioned HPLC laboratory (20 ± 2°C). Before analysis the mobile phase was degassed by use of a Branson sonicator (Branson Ultrasonics, USA) and filtered through a 0.2-µm filter

(Gelman Science, India). Sample solutions were also filtered through a 0.2-μm filter. The system was equilibrated before each injection.

Choice of Internal Standard

To select a suitable internal standard for the analysis, seven drug substances, viz. ketoprofen, probenecid, chlorzoxazone, acetophenone, caffeine, and methyl and propyl parabens, were examined. Among these, acetophenone (Fig. 1) met all the typical requirements of a compound to be used as an IS, i.e. it was stable during the analysis, readily available, was well resolved from PP (R_S 3.98), its peak shape was good (tailing factor 1.24), and its elution time was shorter than that of last eluting analyte peak, DP (saving run time per sample).

Construction of Calibration Plots

Individual stock solutions of DP, PP, and IS were prepared by dissolving the drugs (25 mg, accurately weighed) in 25 mL mobile phase (final concentration 1 mg mL^{-1}). The stock solutions was stored at 4°C protected from light. From this stock solution, 100 μg mL^{-1} standards were freshly prepared for each drug on the day of analysis.

Calibration standards for each analyte were prepared at concentrations of 1, 2, 5, 7, and 10 μg mL^{-1} for PP and 0.5, 1, 2.5, 3.5, and 5.0 μg mL^{-1} for DP. Each calibration standard for PP contained DP at 2.5 μg mL^{-1} and each calibration standard for DP contained PP at 5.0 μg mL^{-1}. All calibration standards for PP and DP contained 25 μg mL^{-1} IS. Separate calibration plots for PP and DP were constructed by plotting PP/IS or DP/IS peak-area ratios against respective concentrations. Unknown assay samples were quantified by reference to these calibration plots. DP solutions of concentration 0.5, 2.5, and 5.0 μg mL^{-1} and PP solutions of concentration 1, 5, and 10 μg mL^{-1} were prepared as quality-control (QC) samples.

Assay Sample Preparation

For assay of DP and PP in capsules, twenty capsules were weighed and their contents were mixed thoroughly. An amount of capsule powder equivalent to 10 mg DP and 20 mg PP was accurately weighed and transferred to a 50-mL volumetric flask. A suitable quantity of IS was added then 25 mL mobile phase. This mixture was sonicated for 10 min, for complete extraction of the drugs, and the solution was diluted to volume with mobile phase to furnish PP, DP, and IS concentrations of 5.0, 2.5, and 25 μg mL^{-1}, respectively. The solution was centrifuged at 4000 rpm for

10 min, the clear supernatant was collected and filtered through a 0.2-μm membrane filter, and 20 μL of the solution was injected for HPLC analysis.

Content Sample Preparation

For assessment of drug-content uniformity in the capsules, the contents of ten capsules were separately transferred to 50-mL volumetric flasks. A suitable quantity of IS was added to each, then 25 mL mobile phase. The mixtures were sonicated then diluted to volume with mobile phase to furnish concentrations of PP, DP, and IS of 5.0, 2.5, and 25 μg mL^{-1} respectively. The solutions were centrifuged, supernatant was collected and filtered, and 20 μL of each solution was injected for HPLC analysis.

Statistical Calculations

Standard regression curve analysis was performed by use of Microsoft Office Excel 2003 software (Microsoft, USA), without forcing through zero. Means and standard deviations were calculated by use of SPSS software version 9.5 (SPSS, Cary, NC, USA). The homoscedasticity for the calibration plots was tested by Cochran's test using Matlab software version 5.1.0.421 (The MathWorks, Natick, MA, USA).

RESULTS AND DISCUSSION

Method Development and Optimisation

Column chemistry, solvent selectivity (solvent type), solvent strength (volume fraction of organic solvent(s) in the mobile phase), additive strength, detection wavelength, and flow rate were varied to determine the chromatographic conditions giving the best separation. The mobile phase conditions were optimised so the peak from the first-eluting compound did not interfere with those from the solvent, excipients, or plasma components. Other criteria, viz. time required for analysis, appropriate k range ($1 < k < 10$) for eluted peaks, assay sensitivity, solvent noise, and use of the same solvent system for extraction of drug from formulation matrices during drug analysis, were also considered. After each change of mobile phase the column was re-equilibrated by passage of at least ten column volumes of the new mobile phase [15].

To investigate the appropriate wavelength for simultaneous determination of DP, PP, and IS, solutions of these compounds in the mobile phase were scanned by UV–visible spectrophotometry (Shimadzu, Japan;

model UV-1601PC) in the range 200–300 nm. From the overlaid UV spectra, suitable wavelength choices considered for monitoring the drugs were 285, 230, and 210 nm (Fig. 2). Solutions of each substance in the mobile phase were also injected directly for HPLC analysis and the responses (peak area) were recorded at 285, 230, and 210 nm. It was observed there was no interference from the mobile phase or baseline disturbance at 285 nm, in contrast with 230 and 210 nm. It was, therefore, concluded that 285 nm is the most appropriate wavelength for analysis of the three substances with suitable sensitivity.

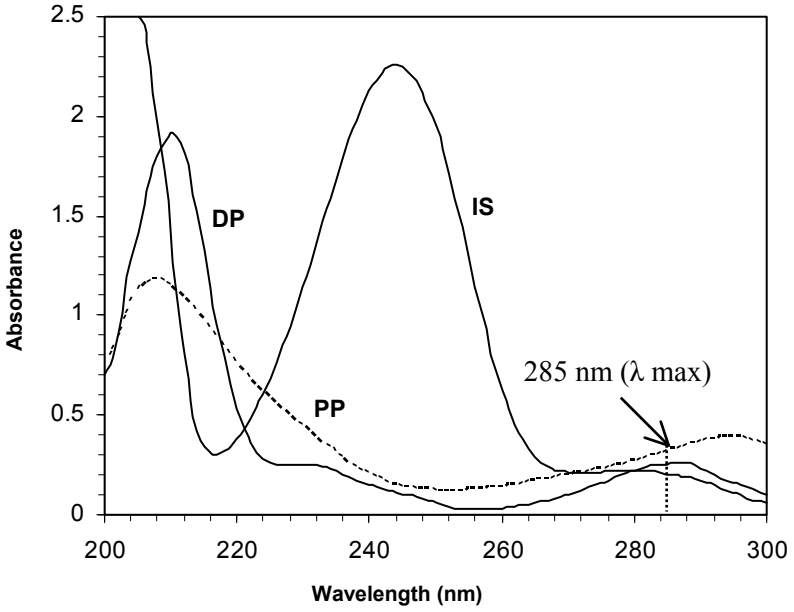

Fig. 2

Overlaid UV spectra of domperidone (DP) at 10.14 μg mL^{-1}, pantoprazole (PP) at 10.11 μg mL^{-1}, and acetophenone (IS) at 10.09 μg mL^{-1}, in the mobile phase

Because the compounds of interest are predominantly polar and of low molecular mass, two reversed-phase columns of different polarity, a C18-Phenomenex (150 mm × 4.6 mm i.d., 5-μm particles) and a CN-Phenomenex (150 mm × 4.6 mm i.d., 5-μm particles) were tried. Several binary mobile phases containing TEA solution (pH 7.0; 10 mM) and ACN (20–55% *v*/*v*) were evaluated with the C_{18} column. The retention times of the solutes decreased with increasing concentration of organic modifier. It was noticed that the *k* value for PP was too low ($k < 1$) at the lowest concentrations of

the organic modifier. In contrast, ACN concentrations which were too high resulted in k values for DP that were too high ($k > 10$) resulting in excessively long runtimes. It is well known that multiple-component mobile phases result in better separation efficiency than binary mobile phases, because with these solvent strength and selectivity can be varied simultaneously to obtain the retention times desired [16,17]. A third component, MeOH, was therefore included in the mobile phase and ternary mixtures of MeOH, ACN, and TEA solution (pH 7.0; 10 mM) in the proportions 30:20:50, 30:25:45, 20:35:45, and 20:33:47 (*v*/*v*) were tried. Use of the last of these resulted in a quality separation in terms of peak symmetry, optimum resolution, reasonable run time, and acceptable k values, particularly for PP (Table I). No further improvement in peak symmetry was observed when a higher TEA concentration (25 mM) was used. Increasing the flow rate from 0.8 to 1.0 mL min^{-1} reduced the run time to less than 10 min. The pH was not varied beyond 7.0, because PP is reported to be unstable below pH 6.0 [18].

Table I

Results from method development and optimisation studies

Property[a]	Compound	Experimental conditions							
		Column[b]		Mobile phase (*v*/*v*)[c]				TEA (mM)[d]	
		C_{18}	CN	30:20:50	30:25:45	20:35:45	20:33:47	10	25
t_R	PP	4.34	2.04	2.48	3.16	2.99	4.34	4.34	4.33
	IS	5.53	2.47	3.49	4.09	4.01	5.52	5.53	5.53
	DP	9.45	3.60	6.03	10.55	6.20	9.46	9.45	9.45
T	PP	1.26	1.47	1.22	1.24	1.35	1.25	1.26	1.25
	IS	1.24	1.38	1.26	1.32	1.34	1.24	1.24	1.24
	DP	1.18	1.26	1.19	1.21	1.25	1.15	1.14	1.15
k	PP	1.89	0.36	0.65	1.11	0.99	1.89	1.89	1.89
	IS	2.67	0.64	1.33	1.73	1.67	2.68	2.67	2.67
	DP	5.30	1.40	3.02	6.03	3.13	5.31	5.30	5.30
N	PP	3573	1869	3426	3429	3498	3625	3529	3648
	IS	4933	2513	4265	4348	4825	4981	4989	4952
	DP	4880	2678	4725	4714	4892	4991	4898	4948

[a] t_R, retention time; T, tailing factor; k, capacity factor; N, number of theoretical plates
[b] The mobile phase was ACN–MeOH–TEA solution (pH 7.0, 10 mM) 20:33:47 (*v*/*v*)
[c] The mobile phase was ACN–MeOH–TEA solution (pH 7.0, 10 mM); C_{18} column
[d] The mobile phase was ACN–MeOH–TEA solution (pH 7.0), 20:33:47 (*v*/*v*); C_{18} column.

To explore the possibility of better separation a CN column was tested with the same mobile phase (20:33:47, *v*/*v*). The order of elution was similar to that on the C_{18} columns (PP < AP < DP) but the retention times were different. Retention of the analytes on the CN columns was much weaker than on C_{18} columns, resulting in unacceptable *k* values (<1) especially for PP. The results listed in Table I suggested the C_{18} column was the best choice because it resulted in acceptable *k* values ($k > 1$), less peak tailing, and greater plate numbers than the CN column. The optimised chromatographic conditions were, therefore, use of the C_{18} column with MeOH–ACN–TEA solution (pH 7.0; 10 mM), 20:33:47 (*v*/*v*) as mobile phase at 1 mL min^{-1}. This method was therefore validated in accordance with ICH guidelines.

Method Validation

System suitability was evaluated by replicate ($n = 6$) injection of the same standard solution containing PP, DP, and the IS at 5.0, 2.5, and 25 μg mL^{-1} respectively. The *RSD* (%) of retention time, peak area, number of theoretical plates, and USP tailing factor for both analytes and the IS were within 1%, indicating the suitability of the system (Table II). The number of theoretical plates and the USP tailing factor were within the acceptance criteria of >2000 and ≤1.5, respectively, indicating good column efficiency and optimum mobile phase composition [15].

Table II

Results from system-suitability study

Property[a]	PP (5 μg mL^{-1})		IS (25 μg mL^{-1})		DP (2.5 μg mL^{-1})	
	Mean[b]	*RSD* (%)	Mean	*RSD* (%)	Mean	*RSD* (%)
t_R	4.35	0.66	5.54	0.39	9.46	0.91
A	303369.15	0.61	354805.24	0.56	127689.25	0.79
T	1.25	0.30	1.24	0.26	1.18	0.31
N	3642	0.71	4961	0.81	4989	0.92

[a] t_R, retention time; *A*, peak area, *T*, tailing factor; *N*, number of theoretical plates
[b] Mean from of six replicate injections ($n = 6$)

Linearity was tested in the concentration range 0.5–5.0 μg mL^{-1} for DP and 1–10 μg mL^{-1} for PP, in the presence of acetophenone (25 μg mL^{-1}) as IS. The solutions were chromatographed six times, in accordance with the International Conference on Harmonization [14]. Separate calibration

plots for PP and DP were constructed by plotting PP/IS and DP/IS peak-area ratios against the respective concentrations, and the method was evaluated by determination of the correlation coefficient and intercept, calculated in the corresponding statistical study (ANOVA; $P < 0.05$). R^2 values >0.999 and intercepts very close to zero confirmed the good linearity of the method. The homoscedasticity for the calibration plots was tested by use of Cochran's test [19], in which the test statistic calculated is the ratio of the largest variance to the sum of all the variances (G = largest variance/sum of variances). The P values calculated for the calibration plots were greater than 0.05, indicating the variances were not significantly different (Table III).

Table III

Linearity and homoscedasticity test for calibration plots

Concentration (μg mL^{-1})	Mean[a] (μg mL^{-1})	*RSD* (%)	Variance (μg mL^{-1})	Cochran's test	
				G value	*P* value[b]
Pantoprazole					
1.0	1.0752	1.6830	0.0003		
3.0	3.0441	0.7950	0.0006		
5.0	4.9057	0.5259	0.0007	0.456	0.117
7.0	7.1305	0.6241	0.0020		
10.0	10.1176	0.2777	0.0008		
Slope	0.1718				
Y intercept	0.0004				
Correlation coefficient	0.9996				
Domperidone					
0.5	0.5173	1.9524	0.0001		
1.5	1.5252	0.9114	0.0002		
2.5	2.4869	0.6112	0.0002	0.472	0.089
3.5	3.5419	0.5393	0.0004		
5.0	4.9408	0.5708	0.0008		
Slope	0.1432				
Y intercept	0.0022				
Correlation coefficient	0.9997				

[a] Mean from six determinations ($n = 6$)
[b] Considered insignificant when $P > 0.05$

Calibration plots were constructed in the very low concentration region (0.05 to 1.0% of the target concentration, i.e. 2.5 to 50 ng mL^{-1} for

PP and 1.25 to 25 ng mL^{-1} for DP) for calculation of the limits of detection (LOD) and quantification (LOQ) using eqs (1) and (2), respectively:

$$\mathrm{LOD} = \frac{3.3\sigma}{S} \quad (1)$$

$$\mathrm{LOQ} = \frac{10\sigma}{S} \quad (2)$$

where σ is the residual standard deviation of the regression line and S is the slope of the standard plot. The values obtained for LOD were 15.3 and 3.0 ng mL^{-1} for DP and PP, respectively; the respective LOQs were 51.0 and 10.1 ng mL^{-1}.

Intra-day accuracy and precision were determined by replicate analysis ($n = 6$) of the QC samples on the same day; inter-day accuracy and precision were determined by replicate analysis of the solutions on six consecutive days. Accuracy was expressed as the bias, i.e. the difference between the results obtained and the reference value. Assay precision was expressed as the relative standard deviation (*RSD*, %). Accuracy and precision calculated for the QC samples from results from intra-day and inter-day analysis are listed in Table IV. Intra-day accuracy ranged from −2.80 to 4.00% and precision from 0.613 to 0.962%. Inter-day accuracy

Table IV

Intra-day and inter-day accuracy and precision of HPLC assay

Reference value (μg mL^{-1})	Intra-day ($n = 6$)			Inter-day ($n = 6$)		
	Mean ± *SD*	Precision (*RSD*, %)	Accuracy (bias, %)	Mean ± *SD*	Precision (*RSD*, %)	Accuracy (bias, %)
Pantoprazole						
1.0	1.02 ± 0.007	0.686	2.00	0.96 ± 0.018	1.875	−4.00
5.0	4.86 ± 0.039	0.802	−2.80	5.14 ± 0.093	1.809	2.80
10.0	10.12 ± 0.062	0.613	1.20	10.42 ± 0.157	1.507	4.20
Domperidone						
0.5	0.52 ± 0.005	0.962	4.00	0.48 ± 0.009	1.875	−4.00
2.5	2.47 ± 0.021	0.850	−1.20	2.61 ± 0.046	1.762	4.00
5.0	5.13 ± 0.049	0.955	2.60	5.16 ± 0.098	1.899	3.20

ranged from −4.00 to 4.00% and precision from 1.507 to 1.899%. Intra-day and inter-day accuracy were within acceptability criteria for bias, ±5%

[20]. Intra-day and inter-day precision was also within acceptability criteria of %*RSD* ≤2.0 and ≤3.0, respectively, indicating method precision was good [21].

The specificity of the method was assessed by comparing the chromatograms obtained from drug standards and from placebo solution prepared from the excipients most commonly used in pharmaceutical formulations, including starch, lactose monohydrate, aerosil, hydroxypropylmethylcellulose, titanium dioxide, and magnesium stearate. No excipient peaks co-eluted with the analytes and IS, indicating the method is selective and specific in relation to the excipients used in this study (Fig. 3).

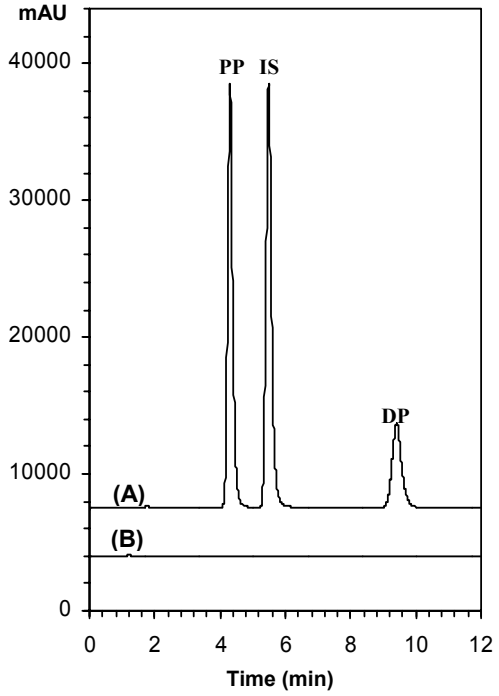

Fig. 3

Chromatograms obtained from (A) a sample (Pantop-D capsule) and (B) a placebo solution. PP, pantoprazole; IS, acetophenone; DP, domperidone

Capsule Assay and Content Uniformity

The method developed in this study was used for determination of the DP and PP content of Pantop-D capsules. Total chromatographic analysis time per sample was 10 min with DP, IS, and PP eluting at retention times of 4.34, 5.52, and 9.46 min, respectively (Fig. 3). Assay results from

three replicate analyses of Pantop-D capsules showed recovery was 100.25 and 101.24% and the *RSD* was 2.95 and 2.81% for PP and DP, respectively.

The results from the content uniformity experiment revealed that the PP and DP content of the ten capsules examined was in the range 98.23–102.12% and 97.89–103.24% and *RSD* was 2.95% and 2.81%, respectively. This indicates that distribution of the drug in the capsules is uniform without significant variation. According to US pharmacopoeia the acceptance limits for drug-content uniformity and *RSD* are 85–115% and <6%, respectively.

There was good agreement between assay results and the label claim of the product. *RSD* values both for multi-capsule potency (composite sample) and for content uniformity testing were <3%. This is indicative both of a well-controlled manufacturing process and a precise analytical method.

CONCLUSIONS

A simple isocratic RP-HPLC method with UV detection has been developed for simultaneous determination of DP and PP. The method was validated for accuracy, precision, specificity, and linearity. The run time is relatively short (10 min), which enables rapid quantification of many samples in routine and quality-control analysis of capsules. The method also uses a solvent system with the same composition as the mobile phase for dissolving and extracting drugs from the matrices, thus minimizing noise. To reduce the cost of analysis and to increase sample throughput during routine analysis the method is being further optimized by statistical experimental design.

REFERENCES

[1] P.M. Laduron and J.E. Leysen, Biochem. Pharmacol., **28**, 2161 (1979)

[2] R.N. Brogden, A.A. Carmine, R.C. Heel, T.M. Speight, and G.S. Avery, Drugs, **24**, 360 (1982)

[3] M. Kobylińska and K. Kobylińska, J. Chromatogr. B, **744**, 207 (2000)

[4] A.P. Zavitsanos, C. MacDonald, E. Bassoo, and D. Gopaul, J. Chromatogr. B, **730**, 9 (1999)
[5] K. Yamamoto, M. Hagino, H. Kotaki, and T. Iga, J. Chromatogr. B, **720**, 251 (1998)
[6] M.S. Nagarsenker, S.D. Garad, and G. Ramprakash, J. Controlled Release, **63**, 31 (2000)
[7] A.P. Argekar and S.J. Shah, J. Pharm. Biomed. Anal., **19**, 813 (1999)
[8] R. Huber, W. Muller, M.C. Banks, S.J. Rogers, P.C. Norwood, and E. Doyle, J. Chromatogr. B, **529**, 389 (1990)
[9] A.M. Mansour and O.M. Sorour, Chromatographia, **53**, S478 (2001)
[10] K. Balmer, B.A. Persson, and P.O. Lagerstrom, J. Chromatogr. A, **660**, 269 (1994)
[11] D. Eberle, R.P. Hummel, and R. Kahn, J. Chromatogr. A, **759**, 185 (1997)
[12] Q.B. Cass, A.L.G. Degani, N.M. Cassiano, and J. Pedrazolli Jr., J. Chromatogr. B, **766**, 153 (2001)
[13] International Conference on Harmonization (ICH), Q2A: Text on Validation of Analytical Procedures: Definitions and Terminology, Vol. 60, US FDA Federal Register, 1995
[14] International Conference on Harmonization (ICH), Q2B: Validation of Analytical Procedures: Methodology, Vol. 62, US FDA Federal Register, 1997
[15] L.R. Snyder, J.J. Kirkland, and J.L. Glajch (Eds), Practical HPLC Method Development, Wiley–Interscience, New York, 1988, pp. 402–438
[16] M. Gazdag, G. Szepesi, and E. Szeleczki, J. Chromatogr., **454**, 83 (1988)
[17] E.H. Jansen, R. Both-Miedema, and R.H. van den Berg, J. Chromatogr., **489**, 57 (1989)
[18] K. Florey (Ed.) Analytical Profiles of Drug Substances and Excipients, Elsevier Science, New York, 2002, pp. 213–259
[19] J.A.M. Pulgarín, A. Molina, and M.T. Pardo, Analyst, **126**, 234 (2001)
[20] R. Sistla, V.S.S.K. Tata, Y.V. Kashyap, D. Chandrasekar, and P.V. Diwan, J. Pharm. Biomed. Anal., **39**, 517 (2005)
[21] S. Ahuja and S. Scypinski (Eds) Handbook of Modern Pharmaceutical Analysis, Academic Press, New York, 2001, pp. 415–443