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Stability indicating simultaneous determination of domperidone (DP), methylparaben (MP) and propylparaben by high performance liquid chromatography (HPLC)

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Abstract

A simple, specific and precise high performance liquid chromatographic method has been developed and validated for the simultaneous determination of methylparaben (MP), propylparaben (PP), and domperidone (DP) in oral suspension. Isocratic mobile phase consists of 0.5% w/v aqueous ammonium acetate buffer:methanol, 40:60 (v/v). Column containing octylsilyl chemically bonded to porous silica particles (Optimapak, OP C8, 150 mm × 4.6 mm, 5 μm, stainless steel analytical column from RS tech) is used as stationary phase. The detection is carried out using variable wavelength UV–vis detector set at 280 nm. The solutions are chromatographed at constant flow rate of 1.0 mL/min. The method separates MP, PP, DP and droperidol (DR) impurity in less than 12 min with good resolution, peak shapes and minimal tailing. Retention times (RT) for MP, PP, DP and DR are about 3.4, 7.0, 9.0 and 10.9 min, respectively. Linearity range and percent recoveries for MP, PP and DP are 90–270, 10–30, 50–1500 μg/mL and 100.30%, 100.78% and 100.48%, respectively. Method was validated according to ICH guidelines and proved to be suitable for stability testing, homogeneity testing and quality control of these compounds in pharmaceutical preparations.

Keywords: Stability indicating; Preservatives; Simultaneous determination; Method validation; Impurities

1. Introduction

Domperidone (DP), 5-chloro-1-[1-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl) propyl]-piperidin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one ($C_{22}H_{24}ClN_5O_2$), is a dopamine antagonist that produces extrapyramidal reactions. It stimulates gastro-intestinal motility and is used as an antiemetic for the short term treatment of nausea and vomiting of various aetiologies, including that associated with cancer therapy and with levodopa or bromocriptine therapy for parkinsonism [1].

Preservatives and preservative systems are crucial part of any oral suspension or syrup formulations containing them. Preservatives such as sodium benzoate, sorbic acid, methylparaben (MP) and propylparaben (PP) have been used for many years. Formulator must be fully aware of the procedure for preservative systems in a product need to be analysed to establish their effectiveness throughout shelf life of the product [2]. Actual concentration of preservative(s) in a formulation is vital in establishing shelf life of the product. Besides, analytical test result of preservative(s) is required by regulatory agencies.

British Pharmacopoeia 2003 (BP' 2003) has described the procedure for assay of raw material domperidone and domperidone maleate by perchloric acid titration and their related substances by HPLC using gradient mixture of ammonium acetate buffer (5 g/L) and methanol as mobile phase at flow rate of 1.5 mL/min, and stainless steel column (10 cm × 4.6 mm) packed with base-deactivated, end-capped octadecylsilyl silica gel for chromatography (3 μm) with detector wavelength set at 280 nm [3]. Determination of domperidone (as domperidone maleate) and its related substances in tablets is performed by HPLC using above chromatographic conditions [3]. This procedure was applied to determine its suitability for use in simultaneous determination of MP, PP, DP and DR using Optimapak, OP C8, 150 mm × 4.6 mm, 5 μm column. But, this resulted in poor resolution between PP, DP and DR peaks. A spectrophotometric method is reported for the determination of

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Table 1
Comparison of system suitability parameters

Parameters	Methylparaben		Propylparaben		Domperidone		Droperidol	
	A	B	A	B	A	B	A	B
Retention time (min)	5.7	3.4	7.8	7.0	8.1	9.0	8.4	11.0
Capacity factor	2.8	1.3	4.2	3.7	4.4	5.0	4.6	6.3
Peak asymmetry	1.12	1.14	1.16	1.15	1.02	0.97	1.02	0.99
Resolution (MP-PP-DP-DR)	–	–	15.5	14.9	3.2	5.4	2.2	4.4
Theoretical plates	26203	5855	65277	8286	75933	7092	81267	8805

A: BP' 2003 domperidone tablets method; B: proposed method.

domperidone and metoclopramide in bulk samples and dosage forms [4]. This method is not suitable for stability analysis of domperidone suspension due to presence of paraben preservatives. Several analytical methods using spectrophotometric [5–7] have been reported for the determination of DP, either alone or in combination with other drugs. Many analytical procedures have been reported for the determination of MP and PP preservatives separately or in combination with other drugs by HPLC and other techniques [8–24]. These methods may not be suitable for simultaneous determination of MP, PP and DP together with DR impurity because of interferences with each other. However, as per bibliographical revisions performed, no HPLC analytical method applied for simultaneous determination of these ingredients containing combination of three component together with droperidol (DR) as impurity, has been found.

Present paper describes a simple, specific, accurate and precise HPLC method for simultaneous determination of MP, PP and DP for use in stability studies and quality control applications associated with these ingredients. The method can also be used for the determination of DR impurity in combination with MP, PP and DP.

Proposed HPLC method is rapid and uses isocratic mobile phase instead of gradient as described in BP' 2003. Suitability of the analytical procedure is demonstrated by its stability indicating ability and optimum chromatographic system suitability parameters, used for the determination of these components. A comparison of system suitability parameters between BP' 2003 method and proposed method is shown in Table 1. Molecular structures of the separated compounds are shown in Fig. 1.

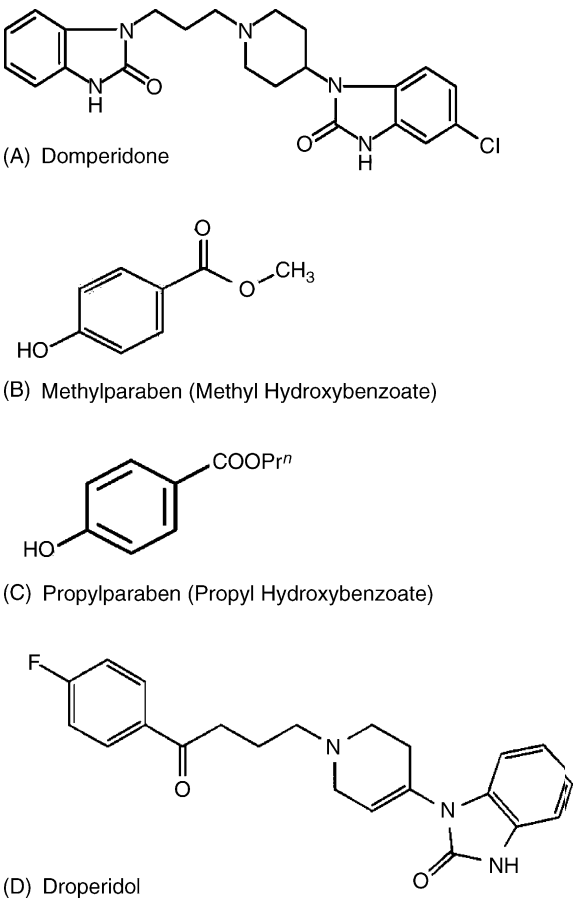

Fig. 1. Molecular structure of the separated compounds.

2. Experimental

2.1. Instrumentation

Integrated high performance liquid chromatographic system LC-2010A from Shimadzu Corporation (Chromatographic and Spectrophotometric Division, Kyoto, Japan) consisted of 4-liquid gradient system, high speed auto-sampler, column oven and UV–vis detector. Optimapak, OP C8, 150 mm × 4.6 mm, 5 μm, stainless steel analytical column from RS Tech, Daejon, Korea, was used as stationary phase. Chromatograms were recorded and integrated on PC installed with Class-VP version 6.13 (Shimadzu, Kyoto, Japan) chromatographic software.

2.2. Reference substances, reagents and chemicals

Domperidone was obtained from Dr. Reddy Laboratories, India. Methylparaben and propylparaben were supplied from Mallinckrodt, England. Ammonium acetate (reagent grade) and hydrochloric acid (reagent grade) and methanol (HPLC grade) were obtained from Panreac Quimica, Spain. Reagent grade *N*,*N*-dimethylformamide (DMF) was obtained from Acros Organics, New Jersey, USA. Distilled water was obtained from a Milli-Q system, Millipore, Milford, MA, USA. Reference standards domperidone and droperidol were obtained from European Pharmacopoeia, Council of Europe, while methylparaben and propylparaben reference standards were obtained from United States Pharmacopoeia Convention, Rockville, MD, USA.

2.3. Chromatographic condition

Isocratic mobile phase consisted of a mixture of 5 g/L solution of ammonium acetate buffer and methanol in the ratio 40:60 (v/v). Mobile phase was filtered and degassed through membrane filter of 0.45 μm porosity under vacuum. Optimapack OP C8, 150 mm × 4.6 mm, 5 μm, stainless steel analytical column was used as stationary phase. Constant flow rate of 1.0 mL/min was employed throughout the analysis. Variable UV–vis detector was set at 280 nm. All analyses were done at ambient room temperature and volume of solution injected on to the column was 10 μL.

2.4. Extraction solvent

DMF was found to be the best solvent to extract domperidone from suspension. Addition of 1.0 mL of 0.1N hydrochloric acid (HCl) helps to precipite the excipients in formulation and enables to obtain clear test solution prior to injection on HPLC for analysis.

2.5. Samples

Test samples were oral suspension manufactured by various manufacturers with following composition per milliliter: MP—1.8, PP—0.2, and DP—1.0 mg and excipients quantity sufficient to produce 1 mL. Other test samples used were accelerated stability samples with similar composition. Samples were treated according to test solution preparation.

2.6. Solution preparation

2.6.1. PP standard stock solution

PP standard stock solution was prepared by transferring 40.0 mg of PP reference standard into 100 mL volumetric flask. A 50 mL portion of methanol was added, sonicated to dissolve and cooled to room temperature. The solution was diluted to volume with methanol and mixed. PP standard stock solution was used to prepare standard solution.

2.6.2. Standard solution

Portions of 20.0 mg of DP and 36 mg of MP reference standards were transferred into 200 mL volumetric flask and dissolved by adding 100 mL of DMF. Further, a 10 mL portion of PP standard stock solution and 2 mL portion of 0.1N HCl were added, volume was completed with methanol to obtain a solution containing 0.10 mg of DP, 0.18 mg of MP and 0.02 mg of PP/mL. The solution was mixed, filtered through 0.45 μm membrane filter and 10 μL was injected.

2.7. Test solution

Sample bottle was shaken by hand to ensure uniform distribution of ingredients prior to transfer. A 10 mL portion of suspension was transferred into 100 mL volumetric flask, taking care to exclude air bubble. To this, a 50 mL portion of DMF and 1 mL portion of 0.1N HCl acid were added. The solution was mixed on vortex mixer for 30 s, sonicated for 5 min and shaken on wrist action shaker for 10 min. Volume was completed by methanol and mixed. The solution was centrifuged at 3500 rpm for 5 min and 10 μL of clear supernatant solution was injected directly on to the column.

2.8. Quantitation

Peak areas were recorded for all peaks. Respective peak areas were taken into account to quantitate the amounts in milligram per milliliter of suspension as follows:

Methylparaben and domperidone

$$\frac{R_{\text{sam}} \times C}{R_{\text{std}} \times 20}$$

Propylparaben

$$\frac{R_{\text{sam}} \times W}{R_{\text{std}} \times 10}$$

where R_{sam} is peak area obtained from MP/DP/PP in the test solution; R_{std} the peak area obtained from MP/DP/PP in the standard solution; C the weight, in mg, of respective MP/DP reference standards taken to prepare standard solution; W the weight, in mg, of PP reference standard taken to prepare propylparaben standard stock solution; numericals 20 and 10 are values obtained from dilution factors of standard and test solution.

3. Results and discussion

3.1. BP' 2003 domperidone tablets assay method

Chromatographic condition prescribed in BP' 2003 under monograph domperidone tablets was used to ascertain its suitability for the determination of domperidone suspension containing DP, MP and PP preservatives, excipients and DR impurity that may have been present in formulation. Mobile phase at flow rate of 1.5 mL/min comprises of mixture of 3 volumes of methanol and 7 volumes of 5 g/L solution of ammonium acetate, changing by linear gradient to methanol over 10 min, followed by elution with methanol for 2 min. Chromatographic procedure is carried out with detector wavelength set at 280 nm and using stainless steel column (10 cm × 4.6 mm) packed with base-deactivated, end-capped octadecylsilyl silica gel for chromatography (3 μm). System suitability requires resolution of at least 2 between DP and DR. These conditions were adopted initially to evaluate MP, PP, DP and DR except to use Optimapak, OP C18, 4.6 mm × 150 mm, 5 μm column (octadecylsilyl). But, none of these compounds were eluted within 12 min run time as stipulated in BP' 2003 method. The procedure was then applied with Optimapak, OP C8, 150 mm × 4.6 mm, 5 μm column (octylsilyl). The retention time (RT) was found to be 5.72 min for MP, 7.76 min for PP, 8.14 min for DP and 8.41 min for DR. MP and PP peaks are eluted with fairly good resolution of 15.5. However, the resolution between PP and DP was 3.2 and that between DP and DR was 2.2. Poor resolution between these peaks may be reduced further over a period of time

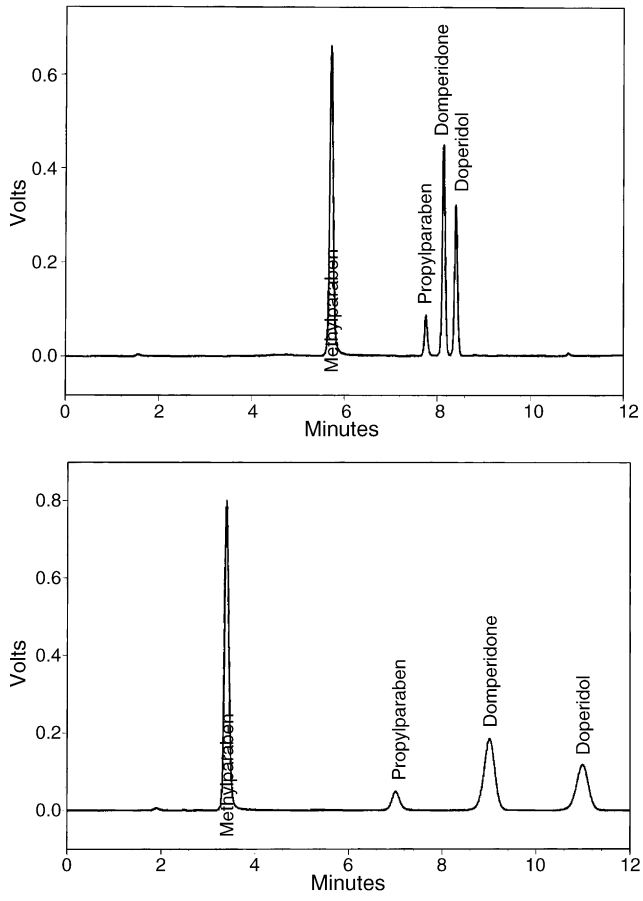

Fig. 2. Comparision of chromatogram showing MP (0.18 mg/mL), PP (0.02 mg/mL), DP (0.10 mg/mL) and DR (0.10 mg/mL) peaks. Top: applied domperidone tablets assay method BP' 2003; Bottom: proposed method.

with increasing column life and thus may cause concern for the accurate quantification of these components. Another factor to consider is the gradient program which may pose problem in meeting the system suitability requirement with minimum resolution of 2 between DP and DR peaks. Chromatograms recorded as per BP' 2003, domperidone tablets assay method and proposed method are shown in Fig. 2.

3.2. Chromatography

Chromatographic system comprising 4 g/L ammonium acetate and methanol (40:60, v/v) at constant flow rate of 1.0 mL/min as mobile phase, Optimapack OP C8, 150 mm × 4.6 mm, 5 μm, stainless steel column as stationary phase, and detector wavelength at 280 nm. This resulted in overlapping peaks of DP and DR at retention time of 2.6 min, but the peaks of MP (RT 3.4 min) and PP (RT 7.0 min) eluted with resolution of 11.5. The mobile phase consisting 5 g/L solution of ammonium acetate and methanol was manipulated and optimized in isocratic condition on the above column to obtain symmetrical peak shapes and good separation between MP and PP (resolution 14.9), PP and DP (resolution 5.4), and DP and DR. Resolution between DP and DR was found to be 4.4, which is almost double the resolution criteria specified in BP'

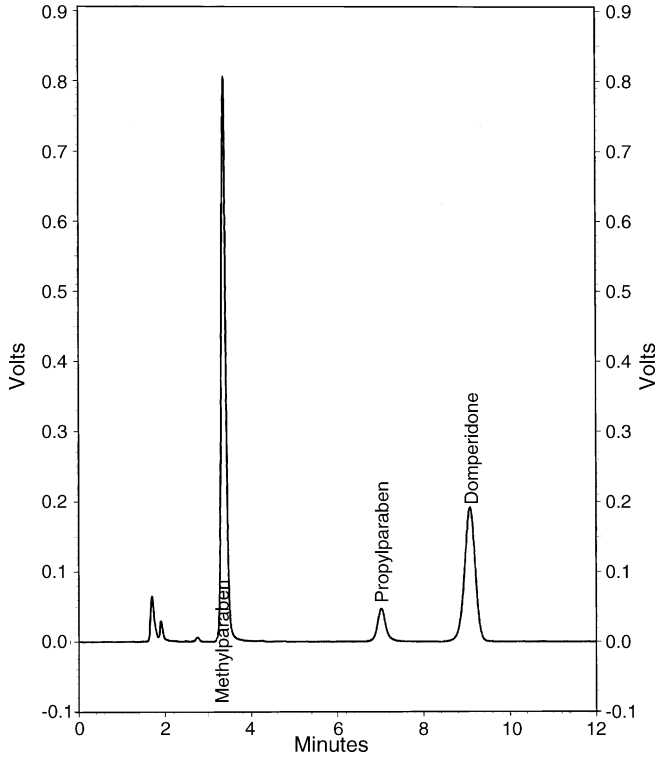

Fig. 3. Chromatogram of Test Solution showing separated peaks of MP, PP and DP.

2003. This was achieved with mobile phase containing mixture of 5 g/L solution of ammonium acetate and methanol in the ratio 40:60 (v/v) at constant flow rate of 1.0 mL/min. Increase in methanol concentration (65%) and decrease in ammonium acetate (35%) in mobile phase resulted in decrease in run time but with lesser resolution between the peaks. It was noted that slight decrease in ammonium acetate (<5 g/L) resulted in decreasing resolution between PP, DP and DR peaks. Fully end-capped derivatised packing of OP C8 column, possibly resulted in symmetrical peak shapes. Detector wavelength set at 280 nm allows sufficient absorption of MP and PP together with DP and DR. Typical chromatogram of test solution is shown in Fig. 3.

3.3. Method validation

Test method for simultaneous determination of MP, PP and DP was validated to include requirements of International Conference on Harmonization (ICH) guidelines [25]. Parameters like specificity, linearity, accuracy, precision, range, robustness and system suitability were examined.

3.4. Specificity

No interferences were observed due to presence of excipients like sacharin sodium, banana flavour and croscarmellose sodium. Principal impurity DR that may have been present in the formulation is separated from main peak of DP with a resolution factor of more than 4.

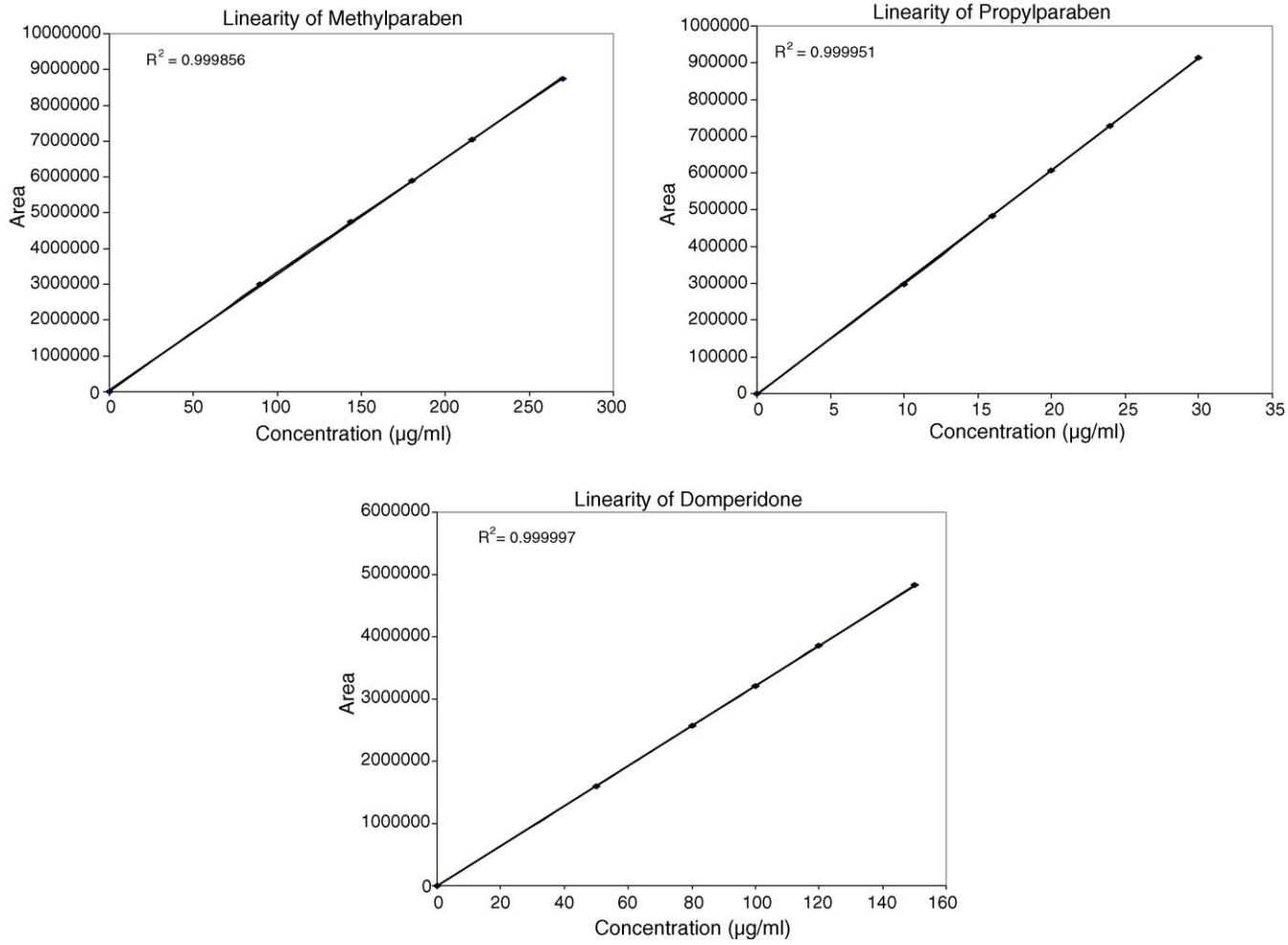

Fig. 4. Linearity graphs of MP, PP and DP.

3.5. Linearity

Peak areas versus concentrations in microgram per milliliter were plotted for MP, PP and DP at the concentration range between 50% and 150% of target level (Fig. 4). MP, PP and DP showed linearity in the range 90–270, 10–30, 50–150 μg/mL, respectively. Linear regression equations and correlation coefficient (R^2) for these linearities are given below:

$$Y_{MP} = 32362x + 46405 \quad (R^2 = 0.999856)$$
$$Y_{PP} = 30491x - 2790.8 \quad (R^2 = 0.999951)$$
$$Y_{DP} = 32176x - 3283.4 \quad (R^2 = 0.999997)$$

3.6. Accuracy

Accuracy and precision of the proposed HPLC determination were evaluated from assay result of components [25]. Accuracy was done by performing the assay of components calculated from peak area responses of different samples by analyte recovery method.

3.6.1. Stock solutions

Stock Solution A was prepared by dissolving accurately weighed portions of 125 mg of DP and 225 mg of MP in DMF to produce 50 mL solution. Stock Solution B was prepared by dissolving accurately weighed portion of 20 mg of PP in DMF to produce 50 mL solution.

Into blank suspension matrix, appropriate portions of MP and DP were spiked with Stock Solution A to provide concentrations of 50%, 75%, 100%, 125% and 150% of target level. Into same matrix containing placebo and MP & DP, portions of PP was spiked with Stock Solution B to provide concentrations of 50%, 80%, 100%, 120% and 150% of target level (Table 2). Mean recovery of spiked samples was 100.30% for MP, 100.78% for PP and 100.48% for DP (Table 3).

3.7. Precision

Instrumental precision was determined by analyzing test sample by six replicate determinations and the relative standard deviations were 0.325% for MP, 0.218% for PP, and 0.387% for DP.

Table 2
Accuracy spiking table (analyte recovery)

No.	Placebo (mL)	Stock Solution A (mL)	Theoretical amount (mg)	Dilution volume (mL)	Final concentration (mg/mL)	Target level concentration (%)
Domperidone						
1	10.0	2.0	5.0	100	0.050	50
2	10.0	3.0	7.5	100	0.075	75
3	10.0	4.0	10.0	100	0.100	100
4	10.0	5.0	12.5	100	0.125	125
5	10.0	6.0	15.0	100	0.150	150
Methylparaben						
1	10.0	2.0	9.0	100	0.090	50
2	10.0	3.0	13.5	100	0.135	75
3	10.0	4.0	18.0	100	0.180	100
4	10.0	5.0	22.5	100	0.225	125
5	10.0	6.0	27.0	100	0.270	150
No.	Placebo (mL)	Stock Solution B (mL)	Theoretical amount (mg)	Dilution volume (mL)	Final concentration (mg/mL)	Target level concentration (%)
Propylparaben						
1	10.0	5.0	1.0	100	0.010	50
2	10.0	8.0	1.6	100	0.016	80
3	10.0	10.0	2.0	100	0.020	100
4	10.0	12.0	2.4	100	0.024	120
5	10.0	15.0	3.0	100	0.030	150

Method precision or intra-assay precision was performed by preparing six different standard solutions involving different weighings and dilutions. Each solution was injected in triplicate under same conditions and mean value of peak area response for each solution were taken. Corrections in area were made for each weight taken to prepare six standard solutions and relative standard deviation of peak area response were calculated from the six solutions. Relative standard deviations were 0.481% for MP, 0.632% for PP and 0.126% for DP.

Intermediate precision was performed by analyzing samples by two different analysts using different instruments. Standard solution and six different samples at 100% target level were prepared by each analyst. Relative standard deviations obtained from 12 assay results by two analysts were 0.439% for MP, 0.467% for PP and 0.581% for DP.

3.8. Range

Range of a method is defined as lower and higher concentrations for which the method has adequate accuracy, precision and linearity.

Table 3
Accuracy data (analyte recovery)

No.	Theoretical amount (mg/mL)	Theoretical (% of target level)	Determined amount (mg/mL)	Determined (% of target level)	Recovered (%)	Bias (%)
Domperidone						
1	0.050	50	0.0507	50.7	101.4	+1.4
2	0.075	75	0.0761	76.1	101.5	+1.5
3	0.100	100	0.1009	100.9	100.9	+0.9
4	0.125	125	0.1244	124.4	99.5	−0.5
5	0.150	150	0.1487	148.7	99.1	−0.9
Methylparaben						
1	0.090	50	0.0898	49.9	99.8	−0.2
2	0.135	75	0.1347	74.8	99.8	−0.2
3	0.180	100	0.1798	99.9	99.9	−0.1
4	0.225	125	0.2267	125.9	100.8	+0.8
5	0.270	150	0.2733	151.8	101.2	+1.2
Propylparaben						
1	0.010	50	0.0101	50.5	101.0	+1.0
2	0.016	80	0.0161	80.5	100.6	+0.6
3	0.020	100	0.0201	100.5	100.5	+0.5
4	0.024	120	0.0242	121.0	100.8	+0.8
5	0.030	150	0.0303	151.5	101.0	+1.0

To demonstrate the range, six samples each of lower concentration (50% of target level) and higher concentration (150% of target level) similar to accuracy samples by spiking drug substance into blank matrix (placebo) were prepared. Each sample was analyzed in duplicate. At lower concentration, mean recovery of MP, PP and DP were found to be 101.3%, 99.5% and 100.2%, respectively. Relative standard deviation obtained from these determinations were found to be 0.54% for MP, 1.32% for PP and 0.92% for DP. At higher concentration, mean recovery of MP, PP and DP were found to be 100.8%, 100.7% and 101.1%, respectively. Relative standard deviation obtained at higher concentration level were found to be 0.68% for MP, 0.77% for PP and 0.74% for DP.

3.9. Robustness

Robustness of proposed method was performed by keeping chromatographic conditions constant with following differences:

i. Changing acetate buffer (35%, v/v) and methanol (65%, v/v) composition in mobile phase.
ii. Increasing the flow rate of mobile phase from 1.0 mL to 1.2 mL/min.
iii. Using another column (Waters, Symmetry C8, 3.9 mm × 150 mm, 5 μm).

Standard solution was injected six times in replicate for each change. System suitability parameters like resolution, peak asymmetry, theoretical plates, capacity factor and relative standard deviation were recorded for each peak and found to be within acceptable limits.

Six test samples at target concentration level were prepared and analyzed in duplicate for each change. Recoveries and relative standard deviations were calculated for each component during each change and found to be 99.0–101.5% and <1.0%, respectively.

3.10. System suitability

System suitability tests were performed to chromatograms obtained from standard and test Solutions to check parameters such as column efficiency, peak asymmetry, capacity factor and resolution between MP, PP, DP and DR peaks. Results obtained from six replicate injections of standard solution as representative chromatograms are summarized in Table 4.

3.11. Determination of droperidol and other impurities

3.11.1. System suitability solution

System suitability solution was prepared by transferring portions of 36 mg of MP, 4 mg of PP, 20 mg of DP and 20 mg of DR into 200 mL volumetric flask. To this, a 100 mL portion of DMF and 2 mL of 0.1N HCl were added. Solution was diluted to volume with methanol and mixed. The solution was filtered through 0.45 μm membrane filter and 10 μL was injected. The resolution between DP and DR must be greater than 2.

3.11.2. Reference solution

Reference stock solution was prepared by transferring a 10 mg portion of DR into 100 mL volumetric flask. A 10 mL portion of DMF was added to dissolve, diluted to volume with methanol and mixed. A 1.0 mL portion of reference stock solution was further transferred into 200 mL volumetric flask. Into this, portions of 2 mL of 0.1N HCl and 100 mL of DMF were added. The solution was diluted to volume with methanol and

Table 4
System suitability parameters

No.	Component	Area	Peak asymmetry	Theoretical plates	Capacity factor	Resolution
1	MP	5934413	1.13	4051	1.23	–
	PP	607062	1.09	6547	3.59	12.87
	DP	3209702	0.94	5721	4.90	4.84
2	MP	5874884	1.13	3993	1.23	–
	PP	610580	1.12	6425	3.60	12.77
	DP	3210317	0.94	5708	4.91	4.83
3	MP	5875685	1.17	4017	1.23	–
	PP	601765	1.10	6487	3.60	12.84
	DP	3211515	0.94	5693	4.91	4.84
4	MP	5861953	1.16	4012	1.23	–
	PP	603387	1.10	6463	3.61	12.85
	DP	3202919	0.94	5721	4.92	4.84
5	MP	5861222	1.16	4005	1.23	–
	PP	602550	1.09	6479	3.61	12.86
	DP	3201826	0.94	5695	4.92	4.84
6	MP	5861695	1.14	3999	1.24	–
	PP	600354	1.10	6440	3.62	12.83
	DP	3207311	0.94	5741	4.95	4.86

mixed. This solution contains 0.5 μg of DR/mL. The solution was filtered through 0.45 μm membrane filter and 10 μL was injected.

3.11.3. Test solution

A 20 mL portion of suspension was transferred into 100 mL volumetric flask. Into this, portions of 50 mL of DMF and 1 mL of 0.1N HCl were added. The solution was mixed on vortex mixer for 30 s, sonicated for 5 min and shaken on wrist action shaker for 10 min. Volume was completed by methanol and mixed to obtain solution containing 360 μg/mL of MP, 40 μg/mL of PP and 200 μg/mL of DP. The solution was centrifuged at 3500 rpm for 5 min and 10 μL of clear supernatant solution was injected directly on to the column.

3.11.4. Interpretation

In the chromatogram obtained with test solution, area due to any secondary peak other than the solvent peak and principal peaks of MP, PP and DP is less than the area of DR peak obtained with reference solution (less than 0.25%). Sum of all secondary peaks is less than twice the area of DR peak obtained with reference solution (less than 0.5%).

4. Conclusion

Proposed HPLC method is rapid, direct, specific, accurate and precise for simultaneous determination of MP, PP and DP from oral suspensions. The method can be used to determine DR and other impurities in oral suspensions containing DP. This method can also be applied for the determination of DP, main impurity DR and other impurities in domperidone tablets. The described method is suitable for stability studies, routine analysis and quality control of oral suspensions or other liquid pharmaceutical preparations and tablets containing these ingredients, either alone or in combination.

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