Original article

SIMPLE AND SELECTIVE SPECTROPHOTOMETRIC METHODS FOR THE DETERMINATION OF DOMPERIDONE IN PHARMACEUTICALS THROUGH CHARGE TRANSFER COMPLEX FORMATION REACTION

Okram ZENITA DEVI, Kanakapura BASAVAIAH*, Kanakapura BASAVAIAH VINAY

University of Mysore, Department of Chemistry, Manasagangotri, Mysore 570006, INDIA

Abstract

Two simple, rapid and selective spectrophotometric methods are described for the determination of domperidone (DOM) in pure drug and in pharmaceuticals. The methods are based on the formation of charge-transfer complex between DOM as n-donor and π-acceptors like 2, 3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in method A or p-chloranilic acid (p-CA) in method B. The products exhibit absorption maxima at 590 and 520 nm in acetone for method A and method B, respectively. Under the optimum reaction conditions, linear relationships with good correlation coefficients (0.998 in method A and 0.999 in method B) were found between the absorbance and the concentration of DOM in the ranges of 5-80 and 20-320 µg/mL in method A and method B, respectively. The apparent molar absorptivity values are calculated to be 4.88×10^3 and 1.14×10^3, L/mol/cm, for method A and method B, respectively, with corresponding Sandell sensitivity values of 0.021 and 0.017 $µg/cm^2$. The limit of detection (LOD) values are found to be 0.28 and 1.19 µg/mL for method A and method B, respectively, with corresponding limit of quantification (LOQ) values of 0.86 and 3.59 µg/mL. The stoichiometry of the reaction was found to be 1:1 in both the cases. The proposed methods were applied successfully for the determination of DOM in tablets with good accuracy and precision. The results obtained by the proposed methods were compared favorably with those of the reference method.

Key words: *Domperidone, Spectrophotometry, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, p-chloranilic acid, Tablets.*

Domperidon'un Farmasötik Preparatlarda Miktar Tayini İçin Yük-Transfer Kompleksi Oluşumuna Dayalı Basit ve Seçici Spektrofotometrik Yöntemler

Domperidon'un (DOM) ham halinde ve farmasötik preparatlar içerisinde miktar tayini için basit, hızlı ve seçici iki adet spektrofotometrik yöntem tanımlanmaktadır. Yöntemler, DOM ile aralarında n-donor ve π-akseptör olarak A yönteminde 2,3-dikloro-5,6-disiyano-1,4-benzokinon (DDQ) ile B yönteminde p-kloroanik asit (p-CA) arasındaki yük transfer komplekslerinin oluşumuna dayanmaktadır. A ve B yöntemlerinde meydana gelen ürünler sırasıyla 590 nm ve 520 nm de maksimum absorbsiyon göstermektedir. Optimum şartlarda, absorbans ile DOM konsantrasyonu arasında A yönteminde 5-80 µg/mL aralığında, B yönteminde 80-320 µg/mL aralığında iyi bir doğrusal ilişki vardır (korelasyon A yönteminde 0.998, B yönteminde 0.999 dur). Molar absorbsiyon katsayısı A ve B yöntemlerinde sırasıyla 4.88×10^3 ve 1.14×10^3 olarak ve Sandell duyarlılığı ise A ve B yöntemlerinde sırasıyla 0.021 ve 0.017 $µg/cm^2$ olarak hesaplanmıştır. A ve B yöntemleri için LOD değerleri sırasıyla 0.28 µg/mL ve1.19 µg/mL ve LOQ değerleri 0.86 µg/mL ve 3.59 µg/mL olarak bulunmuştur. Reaksiyon stokiyometresi her 2 yöntemde de 1:1 olarak bulunmuştur. Önerilen yöntemler tabletlerde DOM miktarı tayini için başarı ile uygulanmıştır. Elde edilen sonuçlar bir referans yöntemi ile elde edilen sonuçlar ile karşılaştırılmıştır.

Anahtar kelimeler: *Domperidon, Spektrofotometri, 2,3-dikloro-5,6-disiyano-1,4-benzokinon, p-kloranilik asit, Tabletler.*

*Correspondence: E-mail: basavaiahk@yahoo.co.in; Fax: 00918212516133

INTRODUCTION

Domperidone (DOM); 5-chloro-1-[1-[3-(2-oxo-2, 3-dihydro-1*H*-benzimidazole-1-yl)propyl]piperidin-4-yl]-1, 3-dihydro-2H-benzimidazol-2-one (Figure 1), is used as an anti-emetic and to suppress nausea and vomiting. DOM is indicated for treating symptoms associated with upper gastrointestinal motility disorders caused by chronic and sub-acute gastritis. It is a gastrointestinal emptying (delayed) adjuvant, a peristaltic stimulant and exhibits antiemetic properties. It can be used in patients with Parkinson's disease (1) and is also found to be effective in the treatment of gastroparesis (2). It is official in BP (3) which recommends non-aqueous titration with perchloric acid as titrant and naphtholbenzein as indicator.
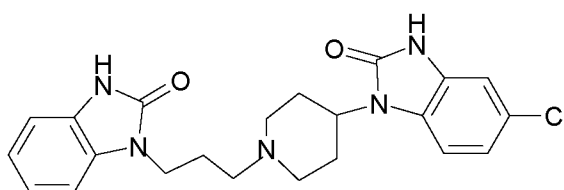
Figure 1. Structure of Domperidone

The therapeutic importance of DOM initiated several reports on its determination, both in pharmaceuticals and in biological fluids. Differential pulse voltammetry (4) and anodic difference pulse voltammetry (5) at a glassy carbon electrode in Britton-Robinson buffer have been used to assay DOM in pharmaceuticals. Application of potentiometric sensors (6) for the analysis of DOM-containing tablets using PVC membrane and carbon paste sensors has also been reported. Planar chromatography (7), high-performance liquid chromatography (8-18) and high-performance thin-layer chromatography (19-23).have been used to assay DOM in pharmaceuticals. For the determination of DOM in biological samples like human, dog and rat plasma, several chromatographic techniques such as liquid chromatography-mass spectrometry (24-26), ultra performance liquid chromatography (27) and high-performance liquid chromatography (28, 29) have been reported. For such applications, however, the operations are time consuming and many of these techniques are deficient in simplicity, cost-effectiveness and easy accessibility.

Spectrophotometry is characterized by its speed and simplicity, accuracy and inexpensive instrument needed, and hence it is an important alternative to other analytical techniques with clear advantages in terms of cost of analysis. The most widely used technique for the assay of DOM has been UV spectrophotometry. Several UV-spectrophotometric (30-43) procedures employing different media have been reported for assay in single as well as in combined dosage forms. Literature survey revealed that there is only one report on the visible spectrophotometric assay of DOM in pharmaceuticals (44) in which four procedures are described. The first two methods are based on redox-complexation reactions involving Fe^{3+}, *o*-phenanthroline and bipyridyl (44) and the other two methods utilize cerium(IV) as the oxidimetric reagent, which subsequently is determined by decrease of red color of chromotrope 2R or orange pink color of Rhodamine 6G (44). The reported four visible spectrophotometric methods (44) involve a heating step and the procedures based on redox-complexation reactions require strict pH control. The present study reports charge-transfer complex formation reaction of DOM with π-acceptors like 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone (DDQ) and *p*-chloranilic acid (*p*-CA) in an attempt to develop simple, selective and reliable

spectrophotometric methods for its determination in tablets. The results obtained were satisfactorily accurate and precise.

EXPERIMENTAL

Apparatus

All absorbance measurements were made on a Systronics model 106 digital spectrophotometer (Ahmedabad, India) provided with 1-cm matched quartz cells. All chemicals and reagents used were of analytical or pharmaceutical grade.

Materials and Reagents
Standard DOM solution

Pharmaceutical grade DOM certified to be 99.85 % was kindly provided by Cipla India Ltd., Mumbai, India and was used as received. A stock standard solution of 400 µg/mL DOM was prepared by dissolving 40 mg of pure drug in 10 mL methanol and diluting to 100 mL in a calibrated flask with acetone and used in method B; and the same was diluted with acetone to get 100 µg/mL DOM for use in method A.

Two brands of tablets containing DOM, Domstal-10 (Torrent Pharmaceuticals Ltd., M. P, India) and Vemistop-10 (Cipla Ltd., H. P., India) used in the investigation were purchased from local commercial sources.

DDQ (0.05 %, w/v)

The solution was prepared by dissolving 0.050 g of *DDQ* (Merck, Mumbai, India) in 100 mL of dioxane.

p-Chloranilic acid (0.1 %, w/v)

The solution was prepared by dissolving 0.100 g of *p*-chloranilic acid (Rolex lab reagents, India) in 100 mL of dioxane.

Procedure for Calibration Curve
Method A

Aliquots of 0.25, 0.5, 1.0, 2.0, 3.0 and 4.0 mL DOM standard solution (100 µg/mL) were transferred into a series of 5 mL calibrated flask. To each flask 1 mL of 0.05 % DDQ solution was added, diluted to the mark with acetone and mixed well. Then, the absorbance was measured at 590 nm against reagent blank treated similarly.

Method B

Varying aliquots (0.25, 0.5, 1.0, 2.0, 3.0 and 4.0 mL) of DOM solution (400 µg/mL) were accurately measured into a series of 5 mL calibrated flasks by means of micro burette. To each flask was added 1 mL of 0.1 % *p*-CA, diluted to the mark with acetone and mixed well. Then, the absorbance was measured at 520 nm against reagent blank treated similarly.

A calibration graph was prepared by plotting the increasing absorbance values *versus* concentration of DOM. The concentration of DOM was read from the calibration graph or computed from the respective regression equation derived using the Beer's law data.

Analysis of commercial tablets

Ten tablets were accurately weighed and powdered. A portion equivalent to 20 mg DOM was accurately weighed and transferred into a 50 mL calibrated flask, 5 mL of methanol and 25 mL of acetone were added to the flask and the content shaken thoroughly for 15-20 min to extract the drug into the liquid phase; the volume was finally diluted to the mark with acetone (50 mL flask), mixed well and filtered using a Whatman No. 42 filter paper. An aliquot of the

filtrate (400 µg/mL DOM) was analysed for DOM following the procedure of method B; and the same solution was diluted with acetone to get a 100 µg/mL DOM and assayed by method A.

Analysis of placebo blank

A placebo blank of the composition: talc (43 mg), starch (35 mg), acacia (25 mg), methyl cellulose (40 mg), sodium citrate (25 mg), magnesium stearate (35 mg) and sodium alginate (30 mg) was made and its solution was prepared in 25 mL calibration flask as described under "analysis of commercial tablets", and then subjected to analysis using the procedures described above.

Analysis of synthetic mixture

To the placebo blank of the composition described above, 20 mg of DOM was added and homogenized, transferred to a 50 mL calibrated flask and the solution was prepared as described under "analysis of commercial tablets", and then subjected to analysis by the procedures described above. The analysis was used to study the interferences of excipients such as talc, starch, acacia, methyl cellulose, sodium citrate, magnesium stearate and sodium alginate.

*Procedure for stoichiometric relationship*

Job's method of continuous variations of equimolar solutions was employed: 1.8783×10^{-3} M each of DOM in acetone and DDQ in dioxane (method A) solutions; and 9.3916×10^{-4} M each of the DOM in acetone and *p*-CA in dioxane (method B) solutions were prepared separately. A series of solutions was prepared in which the total volume of DOM and reagent was kept at 5 mL. The drug and reagent were mixed in various complementary proportions (0:5, 1:4, 2:3, 3:2, 4:1 and 5:0, inclusive) and completed as directed under the recommended procedures. The absorbance of the resultant C-T complex was measured at 590 nm in method A and 520 nm in method B.

RESULTS AND DISCUSSION

π-acceptors like DDQ and *p*-CA are known to yield radical ions *via* charge transfer complexation reaction with a variety of n-donors including amines, iodide ion and metallic salts (45-50). The structural formula of DOM features amino groups; therefore, attempts were made to determine DOM based on the formation of charge-transfer complex with DDQ and *p*-CA as reagents.

Spectral characteristics

Interaction of DOM with DDQ results in the formation of reddish brown color chromogen which exhibits absorption maxima at both 440 and 590 nm (Fig. 2), but 590 nm was selected, because of low blank absorbance and further because the interference from co-formulated substances will generally be far less at longer wavelength. In method B, DOM with *p*-CA yields purple color peaking at 520 nm (Figure 2). In both the wavelengths, reagent blanks showed negligible absorbance values. The predominant chromogen with DDQ or *p*-CA is the colored radical anion that probably resulted through the dissociation of an original donor-acceptor complex (45, 46, 49) with the drug as shown in scheme 1. Abdel-Hamid et al. (45) have also established the formation of DDQ radical anion by electron spin resonance measurements.
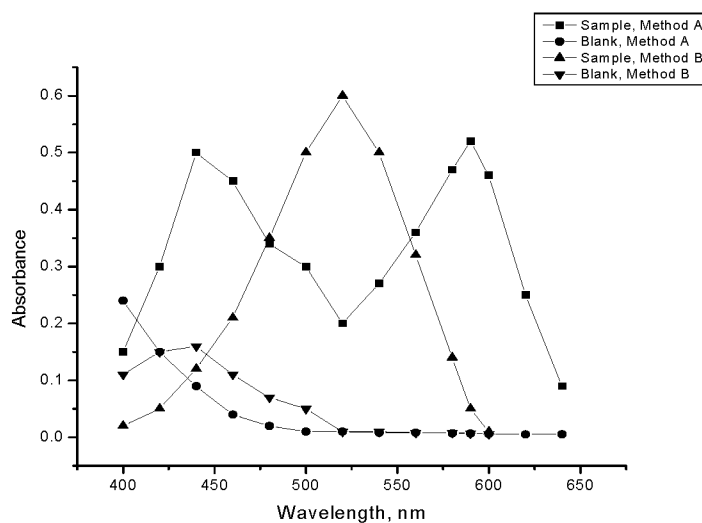
Figure 2. Absorption spectra (40 μg/mL DOM in method A and 240 μg/mL DOM in method B)

Optimization of reaction conditions

    Optimum reaction conditions for quantitative determination of charge transfer complexes were established *via* various preliminary experiments such as choice of organic solvent, concentration of the reagents and reaction time.

Effect of solvent

    The low solubility of the DOM in most of the organic solvents restricted their use, although charge-transfer complexes are formed in those solvents. DOM is easily soluble in methanol; however, charge-transfer reaction between D.OM and DDQ or *p*-CA was not feasible in methanolic medium. Acetone was found to be an ideal solvent to carry out the reactions because it offered excellent solvating power and also possesses high dielectric constant, a property which is known to promote the dissociation of the original charge-transfer complex to the radical ions and dioxane was found to be the best solvent to prepare the DDQ and *p*-CA solutions compared to many other solvents investigated.

Effect of reagent concentration

    The influence of the concentration of DDQ and *p*-CA on the intensity of the color developed at the selected wavelengths was studied. In method A, the absorbance value was unaffected when 0.25-2.0 mL of 0.05% DDQ was used (Figure 3) and reagent blank gave negligible absorbance. Hence, 1 mL of 0.05% DDQ was used for the reaction in method A. In method B, the blank absorbance was found to increase with increasing concentration of *p*-CA. 1 mL of 0.1 % *p*-CA gave maximum absorbance with minimum blank reading (Figure 3). Hence, based on the sensitivity with minimum blank absorbance, 1 mL of 0.1% *p*-CA was fixed in method B.
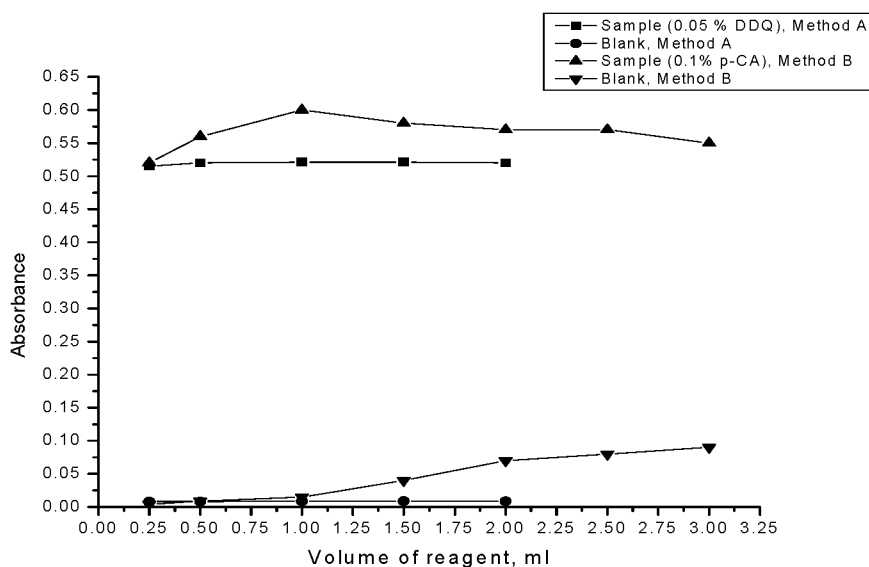
Figure 3. Effect of reagents (40 μg/mL DOM in method A and 240 μg/mL DOM in method B).

Effect of reaction time

The optimum reaction time for the development of color at ambient temperature (30±2°C) was studied and it was found that complete color development was instantaneous in both the methods. The formed color was stable for at least 20 min in both the cases.

Stoichiometric ratio

The molar ratio of DOM to π-acceptor, DDQ or *p*-CA in the complex was determined by applying the Job's method of continuous variations. In both the cases, the plot reached a maximum value at a mole fraction of 0.5 which indicated the formation of 1:1 (DOM: DDQ or *p*-CA) complex (Figure 4). Based on this molar ratio, the colored reaction product can be represented as shown in Figure 5.
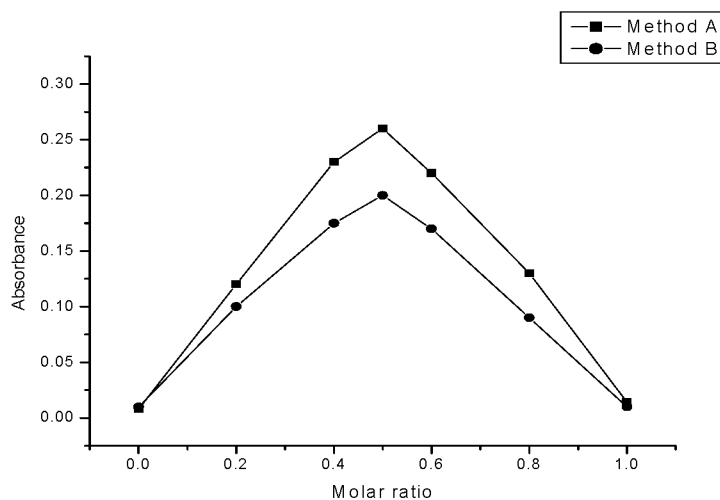
Figure 4. Continuous variation graph for the reaction of DOM with DDQ in method A and with *p*-CA in method B.
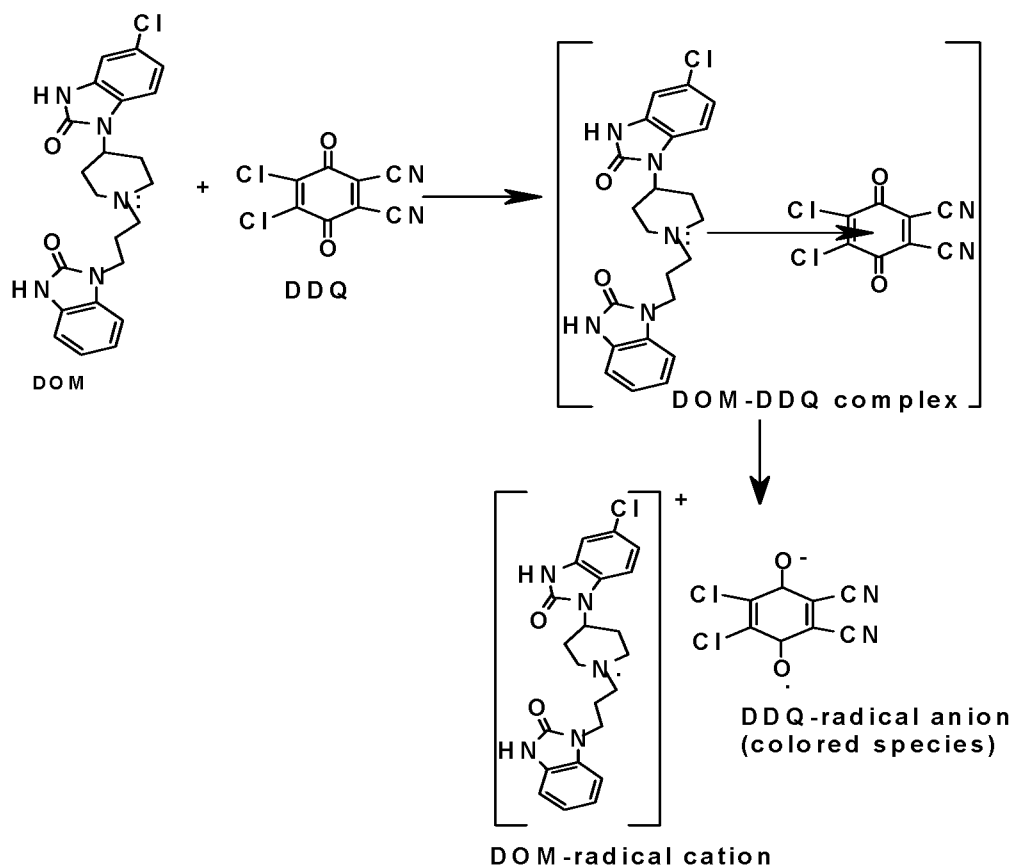
Figure 5. Tentative reaction mechanism

Method validation procedures

The proposed methods have been validated for linearity, sensitivity, precision, accuracy, robustness, ruggedness, selectivity and recovery according to the International Conference on Harmonization (ICH) (51) guidelines.

Linearity and sensitivity

Under optimum conditions, linear relations were obtained between absorbance and concentration of DOM in the range of 5.0-80.0 µg/mL (method A) and 20.0-320.0 µg/mL (method B) (Fig. 7). The calibration graph in each instance is described by the equation:

Y = a + b X

(Where Y = absorbance, a = intercept, b = slope and X = concentration in µg/mL) obtained by the method of least squares. Correlation coefficient, intercept and slope for the calibration data are summarized in Table 1. Sensitivity parameters such as apparent molar absorptivity and sandell sensitivity values, the limit of detection (LOD) and the limit of quantification (LOQ) are calculated as per the current ICH guidelines (51) are compiled in Table 1 speak of the excellent sensitivity of the proposed method. LOD and LOQ were calculated according to the same guidelines using the formulae:

LOD=3.3σ/s and LOQ=10σ/s

where σ is the standard deviation of five reagent blank determinations and s is the slope of the calibration curve.

Table 1. Sensitivity and Regression Parameters.

Parameter	Method A	Method B
λ_{max}, nm	590	520
Linear range, μg/mL	5.0-80	20-320
Molar absorptivity(ε), L/mol.cm	4.88×10^3	1.14×10^3
Sandell sensitivity[a], μg/cm^2	0.087	0.374
Limit of detection (LOD), μg/mL	0.28	1.19
Limit of quantification (LOQ), μg/mL	0.86	3.59
Regression equation, Y^b		
Intercept (a)	0.006	0.008
Slope (b)	0.012	0.002
Standard deviation of a (S_a)	0.021	0.126
Standard deviation of b (S_b)	0.0003	0.0004
Regression coefficient (r)	0.998	0.999

[a]Limit of determination as the weight in μg per mL of solution, which corresponds to an absorbance of A = 0.001 measured in a cuvette of cross-sectional area 1 cm^2 and l = 1 cm. [b]Y=a+bX, Where Y is the absorbance, X is concentration in μg/mL, a is intercept, b is slope.

Precision and accuracy

Intra-day precision and accuracy of the proposed methods were evaluated by replicate analysis (n=7) of calibration standards at three different concentration levels in the same day. Inter-day precision and accuracy were determined by assaying the calibration standards at the same concentration levels on five consecutive days. Precision and accuracy were based on the calculated relative standard deviation (RSD, %) and relative error (RE, %) of the found concentration compared to the theoretical one, respectively (Table 2).

Table 2. Evaluation of intra-day and inter-day accuracy and precision.

Method	DOM taken, μg/mL	Intra-day accuracy and precision (n=7)			Inter-day accuracy and precision (n=7)		
		DOM found, μg/mL	%RE	%RSD	DOM found, μg/mL	%RE	%RSD
Method A (using DDQ)	20	19.70	1.49	2.37	19.64	1.80	2.46
	40	41.10	2.75	2.25	41.16	2.90	2.31
	60	61.72	2.87	2.21	61.80	3.00	2.34
Method B (using *p*-CA)	160	164.0	2.50	1.57	164.7	2.94	2.03
	240	245.6	2.33	1.76	246.3	2.63	1.87
	320	322.1	0.65	1.39	324.3	1.34	2.19

RE: Relative error and RSD: Relative standard deviation.

Robustness and ruggedness

Method robustness was tested by making small incremental change in concentration of DDQ in method A and *p*-CA in method B. To check the ruggedness, analysis was performed by four different analysts; and on three different spectrophotometers by the same analyst. The robustness and the ruggedness were checked at three different drug levels. The intermediate precision, expressed as percent RSD, which is a measure of robustness and ruggedness was within the acceptable limits as shown in the Table 3.

Selectivity

The proposed methods were tested for selectivity by placebo blank and synthetic mixture analyses. A convenient aliquot of the placebo blank solution was subjected to analysis according to the recommended procedures. In both the cases, there was no interference by the inactive ingredients as indicated by the near blank absorbance.

Table 3. Robustness and ruggedness expressed as intermediate precision (%RSD).

Method	DOM taken, µg/mL	Method robustness		Method ruggedness
		Parameter altered		
		DDQ mL[a] in method A or *p*-CA mL[a] in method B, RSD, % (n = 3)	Inter-analysts' RSD,% (n = 4)	Inter-instruments' RSD, % (n = 3)
Method A	20	1.67	1.18	2.16
	40	1.43	1.09	2.29
	60	1.37	1.02	2.32
Method B	160	1.23	1.06	2.41
	240	1.19	0.97	2.26
	320	1.31	1.02	2.35

DDQ and *p*-CA volumes used were 0.8, 1.0 and 1.2 mL in both the methods.

Table 4. Recovery of the drug from synthetic mixture.

Method	DOM in synthetic Mixture taken, µg/mL	DOM recovered* (Percent ± SD)
Method A (using DDQ)	20	112.5 ± 1.37
	40	111.3 ± 1.97
	60	109.2 ± 1.41
Method B (using *p*-CA)	160	104.7 ± 1.52
	240	103.5 ± 1.74
	320	104.2 ± 2.07

*Mean value of five determinations

A separate experiment was performed with the synthetic mixture. The analysis of synthetic mixture solution yielded percent recoveries which ranged of 103.5 -112.5 with standard deviation of 1.37 –2.07 in both the cases. The results of this study are presented in

Table 4 indicating that the inactive ingredients did not interfere in the assay. These results further demonstrate the accuracy as well as the precision of the proposed methods.

Application to analysis of tablets

The proposed methods were successfully applied to the determination of DOM in commercial tablets. The results obtained by the proposed methods were compared to those of the reference method (3) by applying Student's t-test for accuracy and F-test for precision. The reference method describes non-aqueous titration with perchloric acid as titrant and naphtholbenzein as indicator. The results (Table 5) show that the Student's t- and F-values at 95 % confidence level are less than the theoretical values, which confirmed that there is a good agreement between the results obtained by the proposed methods and the reference method with respect to accuracy and precision.

Table 5. Results of analysis of tablets by the proposed methods.

Tablet Brand name	Label claim, mg/tablet	Found[a] (Percent of label claim ± SD) (n=5)		
		Reference method	Method A (using DDQ)	Method B (using *p*-CA)
Domstal-10[b]	10	99.47 ± 1.74	96.46 ± 1.87 t = 2.63 F = 1.16	102.1 ± 1.61 t = 2.48 F = 1.17
vomistop-10 [c]	10	98.13 ±1.62	96.51 ± 1.64 t = 1.57 F = 1.02	99.69 ± 1.74 t = 1.47 F = 1.15

[a]Mean value of five determinations.
[b]Torrent Pharmaceuticals Ltd., M. P, India; [c]Cipla Ltd., H. P., India.
The value of t (tabulated) at 95 % confidence level and for four degrees of freedom is 2.77.
The value of F (tabulated) at 95 % confidence level and for four degrees of freedom is 6.39.

Recovery studies

The accuracy and validity of the proposed methods were further ascertained by performing recovery studies. Pre-analysed tablet powder was spiked with pure DOM at three concentration levels (50, 100 and 150 % of that in tablet powder) and the total was found by the proposed methods. In both the cases, the added DOM recovery percentage values ranged of 104.7-111.46 % with standard deviation of 1.64-2.11 (Table 6) indicating that the recovery was good, and that the co formulated substance did not interfere in the determination.

CONCLUSION

Two new and simple spectrophotometric methods for the determination of DOM in tablets were developed and validated as per the ICH guidelines. The methods are based on well-characterized charge-transfer complexation reactions involving the use of DDQ and *p*-CA as reagents. Compared with most of the existing methods for DOM, the present methods are very simple and cost effective. Of the non-chromatographic methods, the methods based on voltammetric (4, 5) and potentiometric sensor (6) techniques involve rigid pH control. The chromatographic techniques (7-23) although sensitive, require expensive instrumental-set up. A large volume of solvents is required for these techniques, which are expensive, hazardous to health, and harmful to the environment.

Table 6. Accuracy assessment by recovery experiments.

Method	Tablet studied	DOM in tablet, $\mu g/mL$	Pure DOM added, $\mu g/mL$	Total found, $\mu g/mL$	Pure DOM recovered* Percent ± SD
Method A (using DDQ)	Vemistop-10	19.3	10	30.45	111.5 ± 1.81
		19.3	20	40.97	108.4 ± 2.11
		19.3	30	50.71	104.7 ± 2.06
Method B (using *p*-CA)	Vemistop-10	79.75	40	123.75	110.0 ± 1.64
		79.75	80	165.59	107.3 ± 1.76
		79.75	120	206.35	105.5 ± 1.88

[a]Mean value of three measurements.

Most of the UV-spectrophotometric methods (30-43) are less sensitive and applicable to multi component mixture. The reported four visible spectrophotometric methods (44) require boiling for 5-10 min and in addition to this, the procedures based on redox-complexation reaction also require strict pH control.

In contrast to the above published methods, the present methods can be applied at ambient temperature, color development is instantaneous and neither involves complicated extraction procedure nor requires strict pH control. Although the proposed methods seem less sensitive than some of the published methods, measurement is made at longer wavelengths in both the methods. This is a decisive advantage since the interference from co-formulated substances will generally be far less at longer wavelength.

ACKNOWLEDGEMENTS

REFERENCES

1. Shindler JS, Finnerty GT, Towlson K, Dolan AL, Davies CL, Parkes JD, Domperidone and levodopa in parkinson's disease, Br J Clin Pharmacol 18(6), 959–962, 1984.
2. Silvers D, Kipnes M, Broadstone V, Domperidone in the management of symptoms of diabetic gastroparesis: efficacy, tolerability, and quality-of-life outcomes in a multicenter controlled trial, DOM-USA-5 Study Group Clin Ther 20(3), 438–53, 1998.
3. British Pharmacopoeia, The Stationary Office London, p. 572, 2009.
4. El-Shahawi MS, Bahaffi SO, El-Mogy T, Analysis of domperidone in pharmaceutical formulations and wastewater by differential pulse voltammetry at a glassy-carbon electrode, Anal Bioanal Chem 387(2), 719-725, 2007.
5. Wahdan T, Abd El-Ghany N, Determination of domperidone in tablet dosage form by anodic differential pulse voltammetry, IL_Farmaco 60(10), 830-833, 2005.
6. Girish Kumar K, Augustine P, John S, Novel potentiometric sensors for the selective determination of domperidone, J Appl Electrochem 40(1), 65-71 2010.

7. Seema AG, Atul AS, Yogini SJ, Sanjay JS, Quantitative planar chromatographic analysis of pantoprazole sodium sesquihydrate and domperidone in tablets, J Planar Chromatogr-Mod TLC 19(110) 302-306, 2006.
8. Sivakumar T, Manavalan R, Valliappan K, Development and validation of a reversed-phase HPLC method for simultaneous determination of domperidone and pantoprazole in pharmaceutical dosage forms, Acta Chromatogr 18, 130-142, 2007.
9. Veronique M, Chantal S, Jacques T, An improved HPLC assay with fluorescence detection for the determination of domperidone and three major metabolites for application to in vitro drug metabolism studies, J Chromatogr B 852(1-2), 611-616, 2007.
10. Kalirajan R, Anandarajagopal K, Mary Mathew S, Gowramma B, Jubie S, Suresh B, Simultaneous determination of rabeprazole and domperidone in dosage forms by RP-HPLC, Rasayan J Chem 1(2) 232-235, 2008.
11. Patel BH, Suhagia BN, Patel MM, Patel JR, Determination of Pantoprazole, Rabeprazole, Esomeprazole, Domperidone and Itopride in Pharmaceutical Products by Reversed Phase Liquid Chromatography Using Single Mobile Phase, Chromatographia 65(11-12), 743-748, 2007.
12. Patel B, Dedania Z, Dedania R, Ramolia C, Vidya Sagar G, Mehta RS, Simultaneous Estimation of Lansoprazole and Domperidone in Combined Dosage Form by RP-HPLC, Asian J Research Chem 2(2), 210-212, 2009.
13. Sivasubramanian L, Anilkumar V, Simultaneous HPLC estimation of omeprazole and domperidone from tablets, Indian J Pharm Sci 69(5), 674-676, 2007.
14. Patel BH, Patel MM, Patel JR, Suhagia BN, HPLC analysis for simultaneous determination of rabeprazole and domperidone in pharmaceutical formulation, J Liq Chromatogr Rel Technol 30(3), 439 – 445, 2007.
15. Karthik A, Subramanian G, Ranjith Kumar A, Udupa N, Simultaneous estimation of paracetamol and domperidone in tablets by reverse phase HPLC method, Indian J Pharm Sci 69(1), 142-144, 2007.
16. Argekar AP, Shah SJ, Simultaneous determination of cinnarizine and domepiridone maleate from tablet dosage form by reverse phase ion pair high performance liquid chromatography, J Pharm Biomed Anal 19(6), 813-7, 1999.
17. Sabnis SS, Dhavale ND, Jadhav VJ, Gandhi SV, Column reversed-phase high-performance liquid chromatographic method for simultaneous determination of rabeprazole sodium and domperidone in combined tablet dosage form, J AOAC Int 91(2), 344-348, 2008.
18. Thanikachalam S, Rajappan M, Kannappan V, Stability-indicating HPLC method for simultaneous determination of pantoprazole and domperidone from their combination drug product, Chromatographia 67(1-2), 41-47, 2008.
19. Patel BH, Suhagia BN, Patel MM, Patel JR, Simultaneous estimation of pantoprazole and domperidone in pure powder and a pharmaceutical formulation by high-perfomance liquid chromatography and high-performance thin-layer chromatography methods, J AOAC Int 90(1), 142-6, 2007.
20. Patel BH, Suhagia BN, Patel MM, Patel JR, HPTLC determination of rabeprazole and domperidone in capsules and its validation, J Chromatogr Sci 46(4), 304-7, 2008.
21. Patel BH, Patel MM, Patel JR, Suhagia BN, Simultaneous determination of omeprazole and domperidone in capsules by RP-HPLC and densitometric HPTLC, J Liq Chromatogr Rel Technol 30(9-12), 1749-1762, 2007.
22. Yadav A, Raman Singh M, Satish Mathur C, Pawan Saini K, Gyanendra Singh N, A simple and sensitive HPTLC method for simultaneous analysis of domperidone and paracetamol in tablet dosage forms, J Planar Chromatogr Mod TLC 22(6) 421-424, 2009.
23. Susheel JV, Lekha M, Ravi TK, High performance thin layer chromatographic estimation of lansoprazole and domperidone in tablets, Indian J Pharm Sci 69 (5), 684-686, 2007.
24. Wu MS, Gao L, Cai XH, Wang GJ, Determination of domperidone in human plasma by LC-MS and its pharmacokinetics in healthy Chinese volunteers, Acta Pharmacol Sin 23 (3), 285-8, 2002.

25. Zhan L, Jing Y, Ziqiang Z, Luyong Z, Simultaneous determination of omeprazole and domperidone in dog plasma by LC-MS method, J Chromatogr Sci, 47(10), 881-884, 2009.

26. Bose A, Bhaumik U, Ghosh A, Chatterjee B, Chakrabarty US, Sarkar AK, Pal TK, LC-MS simultaneous determination of itopride hydrochloride and domperidone in human plasma, Chromatographia 69(11-12),1233-1241, 2009.

27. Dong-Hang X, Hong-Gang L, Hong Y, Bo J, Quan Z, Zhong-Miao Z, Zou-Rong R, Quantitative determination of domperidone in human plasma by ultraperformance liquid chromatography with electrospray ionization tandem mass spectrometry, Biomed Chromatogr 22(4), 433 – 440, 2008.

28. Koujirou Y, Mami H, Hajime K, Tatsuji I, Quantitative determination of domperidone in rat plasma by high-performance liquid chromatography with fluorescence detection, J Chromatogr B 720(1-2), 251-255, 1998.

29. Sivakumar T, Manavalan R, Valliappan K, Computer-assisted optimization of liquid-liquid extraction for HPLC analysis of domperidone and pantoprazole in human plasma, Acta Chromatogr 20(4), 549-562, 2008.

30. Al-khamis KI, Hagga MEM, Al-khamees HA, Al-awadi M, Spectrophotometric determination of domperidone using δA method, Anal Lett, 23(3), 451 – 460, 1990.

31. Sherje AP, Kasture AV, Gujar KN, Yeole PG, Simultaneous spectrophotometric determination of lansoprazole and domperidone in capsule dosage form, Indian J Pharm Sci 70(1), 102-105, 2008.

32. Shweta Sabnis S, Nilesh Dhavale D, Vijay Jadhav Y, Santosh Tambe R, Santosh Gandhi V, Spectrophotometric simultaneous determination of rabeprazole sodium and domperidone in combined tablet dosage form, Eurasian J Anal Chem 3(2), 236-244, 2008.

33. Mohamed ME, al-Khamees HA, Al-Awadi M, Al-Khamis KI, Spectrophotometric simultaneous determination of rabeprazole sodium and domperidone in combined tablet dosage form, Farmaco 44(11),1045-52, 1989.

34. Kapil K, Naik S, Garima J, Mishra N, Spectrophotometric method for simultaneous estimation of paracetamol and domperidone in tablet formulation, Asian J Research Chem 2(2), 112-114, 2009.

35. Rajendraprasad Y, Rajasekhar K K, Shankarananth V, Yaminikrishna HV, Saikumar S, Venkata raghav reddy P, Spectrophotometric method for the estimation of domperidone in bulk and pharmaceutical formulations, J Pharm Res 2(10), 1593-1594, 2009.

36. Maissa Salem Y, Mohamed El-Bardicy G, Mohamed El-Tarras F, Eman El-Zanfally S, Simultaneous determination of domperidone maleate and cinnarizine in a binary mixture using derivative ratio spectrophotometry and classical least squares calibration, J Pharm Biomed Anal 30(1), 21-33, 2002.

37. Lakshmana SP, Shirwaikar A, Shirwaikar A, Dinesh Kumar C, Joseph A, Kumar R, Lakshmana L, Simultaneous Estimation of esomeprazole and domperidone by UV Spectrophotometric Method, Indian J Pharm Sci 70(1), 128-131, 2008.

38. Sahu R, Preeti N, Bhattacharya S, Deepti J, Simultaneous spectrophotometric estimation of famotidine and domperidone in combined tablet dosage form, Indian J Pharm Sci 68(4), 503-506, 2006.

39. Sherje A, Kasture A, Gujar K, Yeole P, Simultaneous spectrophotometric determination of lansoprazole and domperidone in capsule dosage form, Indian J Pharm Sci 70(1), 102-105, 2008.

40. Salem MY, El-Zanfaly ES, El-Tarras MF, El-Bardicy MG, Simultaneous determination of domperidone and cinnarizine in a binary mixture using derivative spectrophotometry, partial least squares and principle component regression calibration, Anal Bioanal Chem 375(2), 211-6, 2003.

41. Ravi Kumar P, Bhanu Prakash P, Murali Krishna M, Santha Yadav M, Asha Deepthi C, Simultaneous estimation of domperidone and pantoprazole in solid dosage form by UV spectrophotometry EJ Chem 3 (3),142- 145, 2006.

42. Charde , Walode, S, Tajne M, Kasture A, Simultaneous estimation of ranitidine and domperidone in combined dosage form, Indian J Pharm Sci 68(5), 660-662, 2006.
43. Charde M, Walode S, Tajne M, Kasture A, UV-spectrophotometric estimation of ranitidine and domperidone in tablet formulations, Indian J Pharm Sci 68(5), 658-659, 2006.
44. Alaa Amin S, Gamal Ragab H, Spectrophotometric methods for the determination of anti-emetic drugs in bulk and in pharmaceutical preparations, Anal Sci 19(5), 747, 2003.
45. Abdel-Hamid ME, Abdel-Salam M, Mahrous MS, Abdel-Khalek MM, Utility of 2,3-dichloro-5,6-dicyano-p-benzoquinone in assay of codeine, emetine and pilocarpine, Talanta 32 (10) 1002-1004, 1985.
46. Hissam EA, Utility of certain π-acceptors for Spectrophotometric determination of perindopril, J Pharm Biomed Anal 17(8), 1267-1271, 1998.
47. Elmorsy K, Spectrophotometric determination of terfenadine in pharmaceutical preparations by charge-transfer reactions, Talanta 75(5), 1167-1174, 2008.
48. Sayed IMZ, Two charge-transfer complex spectrophotometric methods for the determination of sulpiride in pharmaceutical formulations, Cent Eur J Chem 7(4), 870-875, 2009.
49. Asad R, Tariq Mahmood A, Shahida BN, A novel spectrophotometric method for the determination of zolmitriptan in pharmaceutical formulations, J Chin Chem Soc 54(6), 1413-1417, 2007.
50. Azza AM, Lories IB, Heba HR, Spectrophotometric determination of clobetasol propionate, halobetasol propionate, quinagolide hydrochloride, through charge transfer complexation, J Pharm Biomed Anal 27(6), 889-899, 2002.
51. International Conference On Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Validation of Analytical Procedures: Text and Methodology Q2(R 1), Complementary Guideline on Methodology dated 06 November 1996, incorporated in November 2005, London.