Asian Journal of Chemistry; Vol. 25, No. 13 (2013), 7377-7380

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2013.14679

Spectrophotometric Determination of Domperidone in its Pharmaceutical Formulation Through Charge Transfer Complexation Reactions

NAWAL A. ALARFAJ*, AZZA A. MOSTAFA and ZINAH A. AL-GHAMDI

Department of Chemistry, College of Science, King Saud University, P.O. Box 22452, Riyadh 11495, Saudi Arabia

*Corresponding author: Tel/Fax: +96 614772245; E-mail: nalarfaj@hotmail.com

(*Received*: 15 October 2012; *Accepted*: 28 June 2013) AJC-13711

Two simple, precise and accurate spectrophotometric methods have been developed for determination of domperidone in bulk drug and in its pharmaceutical formulation. The methods are based on the formation of charge-transfer complex between domperidone as π-donor and a π-acceptor like 2,3-dichloro-5,6-dicyano-l,4-benzoquinone in method (**1**) or a σ-acceptor like iodine in method (**2**). The products exhibit absorption maxima at 458 nm in acetonitrile for method (**1**) and at 394 nm in chloroform for method (**2**), respectively. Under the optimum reaction conditions, linear relationships with good correlation coefficients (0.9999 for both methods) were found between the absorbance and the concentration of domperidone in the range of 10-70 µg/mL in both methods. The limit of detection values are found to be 1.26 and 1.14 µg/mL for method (**1**) and method (**2**), respectively, with corresponding limit of quantification values of 4.20 and 3.80 µg/mL. The stoichiometry of the reaction was found to be 1:1 in both methods. The proposed methods were applied successfully for the determination of domperidone in motilium 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-l,4-benzoquinone, Iodine, Tablets.

INTRODUCTION

Domperidone (DM); 5-chloro-1-[1-[3-(2-oxo-2,3-dihydro-1*H*-benzimidazole-1-yl)propyl]piperidin-4-yl]-1,3-dihydro-2*H*-benzimidazol-2-one (Fig. 1), is used as an antiemetic and to suppress nausea and vomiting. Domperidone 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 officialed in BP[3] which recommends non-aqueous titration with perchloric acid as titrant and naphtholbenzein as indicator.

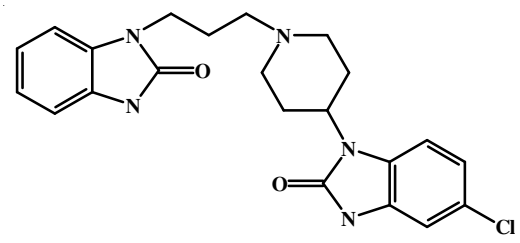

Fig. 1. Chemical structure of domperidone

The therapeutic importance of domperidone 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 domperidone in pharmaceuticals. Application of potentiometric sensors[6] for the analysis of domperidone-containing tablets using PVC membrane and carbon paste sensors has also been reported. Planar chromatography[7], high-performance liquid chromatography[8-10], high-performance thin-layer chromatography[11,12], liquid chromatography-mass spectrometry[13] and ultra performance liquid chromatography[14] have been reported for its determination. For such applications, however, the operations are time consuming and many of these techniques are deficient in simplicity, cost-effectiveness and easy accessibility.

One spectroflurimetric method was reported for the simultaneous determination of domperidone in pharmaceuticals and biological fluids[15].

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 domperidone has been UV spectrophotometry. Several UV-spectrophotometric[16-18]

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 two reports on the visible spectrophotometric assay of domperidone in pharmaceuticals[19,20]. In the first method[19], four procedures were described. The first two procedures are based on redox-complexation reactions involving Fe^{3+}, *o*-phenanthroline and bipyridyl and the other two procedures utilize cerium(IV) as the oxidation reagent, which subsequently is determined by decrease of red colour of chromotrope 2R or orange pink colour of rhodamine 6G. These methods involve a heating step and the procedures based on redox-complexation reactions require strict pH control. The second method[20] was recently reported and describes two procedures for domperidone determination in pharmaceuticals through charge-transfer complex formation reactions of domperidone with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and *p*-chloranilic acid as π-acceptors and measurement of the absorption maxima at 590 and 520 nm in acetone, respectively. The aim of the present study was to develop new, simple, sensitive and reliable visible spectrophotometric methods for the fast control analysis of domperidone in pure form and in its dosage form based on the formation of charge-transfer complexes of domperidone with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone as a π-acceptor in acetonitrile and with iodine as a σ-acceptor in chloroform.

EXPERIMENTAL

Spectral runs were made on a Unicam UV-VIS spectrometer, Helios Alpha: Helios Beta model with 1 cm cuvette (Biochrom, England). Pure domperidone was obtained from Janssen Pharmaceutica Co./Belgica and was used as received. Pharmaceutical formulation was obtained from local market, as Motilium tablets (10 mg domperidone/tablet), Batch No.: 02JB997) Janssen-Cilag. All chemicals used were of analytical reagent-grade quality and solvents were of spectroscopic grade. Distilled water was used throughout this work. Aqueous solutions of the following reagents were used: 0.4 % (w/w) 2,3-dichloro-5,6-dicyano-l,4-benzoquinone (DDQ) (FLUKA) was prepared in acetonitrile (BDH), 0.1 M iodine (Carlo Erba, Divisione Chemica Industriale-Milano) was prepared in chloroform (BDH).

Standard solutions: Standard stock solutions of pure domperidone must be freshly prepared for corresponding methods.

For method (1): (1.0 mg/mL) was prepared by dissolving 10 mg of pure domperidone in acetonitrile in a 10 mL volumetric flask and diluted with the same solvent to the mark.

For method (2): (1.0 mg/mL) was prepared by dissolving 10 mg of pure domperidone in chloroform in a 10 mL volumetric flask and diluted with the same solvent to the mark.

Construction of calibration curves: Calibration curves were constructed according to the optimum conditions in Table-1.

Method (1): In a series of 10 mL volumetric flasks, different aliquots of stock domperidone solution in acetonitrile were transferred to provide final concentration range 10-70 μg/mL. To each flask, 2 mL of 0.4 % DDQ reagent solution were added. Each solution was made up to the mark with acetonitrile and the absorbances of the reddish brown coloured solutions were measured against a reagent blank at 458 nm.

TABLE-1
OPTICAL AND REGRESSION CHARACTERISTICS OF DOMPERIDONE USING THE PROPOSED METHODS

Parameter	Method (1) (DDQ)	Method (2) (I_2)
λ_{max} (nm)	458	394
Linearity range (μg/mL)	10-70	10-70
Detection limit (μg/mL)	1.26	1.14
Quantification limit (μg/mL)	4.2	3.8
*Regression equation:		
Slope (b)	0.01	0.011
Intercept (a)	0.0676	0.094
Correlation coefficient (r)	0.9999	0.9999

*With respect to A = a + bC where C is concentration of drug in (μg/mL) and A is absorbance.

Method (2): In a series of 10 mL volumetric flasks, different aliquots of domperidone standard solution in chloroform equivalent to 10-70 μg/mL were transferred. 2 mL of 0.1 M I_2 reagent solution were added. Each solution was left a side for 20 min for completion of reaction then made up to the mark with chloroform and the absorbances of the coloured solutions were measured against a reagent blank at 394 nm. In either method, a calibration curve was prepared by plotting the absorbance as a function of concentration of drug solution. Alternatively, the corresponding regression equation was derived.

Procedure for pharmaceutical formulation

Method (1): Ten tablets were weighed and finely powdered. An amount of powder equivalent to 10 mg of domperidone was dissolved in 5 mL of acetonitrile, filtered in a 10 mL volumetric flask then completed to volume with acetonitrile and proceeded as described for method (**1**) using the standard addition method.

Method (2): An accurately weighed amount of the powder of 10 pulverized tablets equivalent to 10 mg of domperidone was dissolved in 5 mL of chloroform, filtered in a 10-mL volumetric flask and the volume was completed to the mark with chloroform, then it was proceeded as described for method (**2**) using the standard addition method.

In either method, the nominal content of tablets was calculated either from the previous plotted calibration graph or by using the regression equation.

Procedure for stoichiometric relationship: Job's method of continuous variations of equimolar solutions was employed: 2.348×10^{-4} M each of domperidone and DDQ in acetonitrile (method **1**) solutions and 2.348×10^{-4} M each of domperidone and I_2 in chloroform (method **2**) solutions were prepared separately. A series of solutions was prepared in which the total volume of domperidone and reagent was kept at 10 mL. The drug and reagent were mixed in various complementary proportions (1:9, 2:8, 3:7, 4:6, …, 9:1, inclusive) and completed as directed under recommended procedures. The absorbance of the charge-transfer complexes were measured at 458 nm in method (**1**) and at 394 nm in method (**2**).

RESULTS AND DISCUSSION

Method (1): Domperidone has a pair of π-electrons mainly exists on the tertiary nitrogen atom of the pyridine ring which can be donated to π-acceptor or σ-acceptor compounds. π-Acceptors such as DDQ and σ-acceptors like

I_2 are known to yield radical ions *via* charge transfer complexation reaction with a variety of *n*-donors including amines, iodide ion and metallic salts[21,22]. The structural formula of domperidone features amino groups, therefore, attempts were made to determine domperidone based on the formation of charge-transfer complex with DDQ and I_2 as reagents.

Interaction of domperidone with DDQ results in the formation of a reddish brown colour chromogen which exhibits absorption maxima at 410, 458 and 495 nm (Fig. 2), the absorbance at both 458 and 495 nm was approximately identical but 458 nm was selected, because of low blank absorbance. In method (**2**), domperidone with I_2 yields a yellow colour complex peaking at multi wavelengths but 394 nm was chosen as it gives highest absorbance and more intensive colour (Fig. 3). The predominant chromogen with DDQ or I_2 is the coloured radical anion that probably resulted through the dissociation of an original donor-acceptor complex[21,22] with the drug as shown in **Schemes I** and **II**.

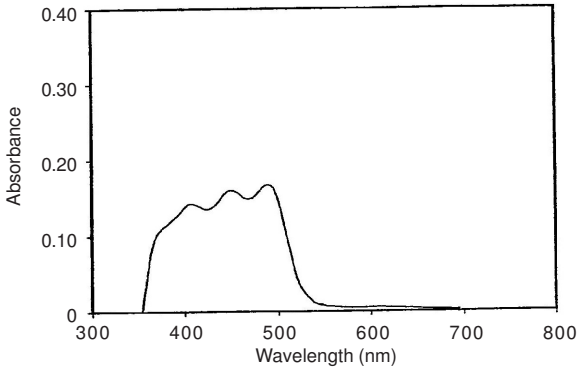

Fig. 2. Absorption spectrum of (10 µg/mL) domperidone/DDQ charge-transfer complex in acetonitrile

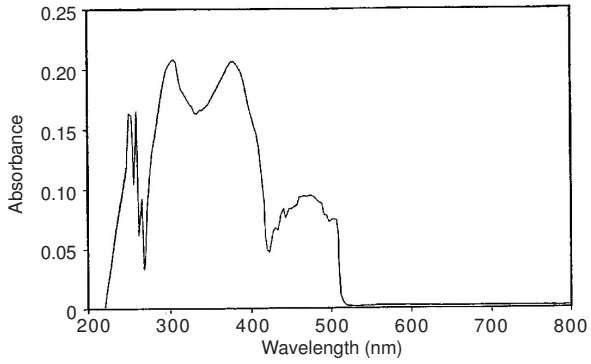

Fig. 3. Absorption spectrum of (10 µg/mL) domperidone /I_2 charge-transfer complex in chloroform

$$\underset{\text{Domperidone (n-donor)}}{\ddot{D}} + \underset{\text{DDQ } (\pi\text{-acceptor})}{A} \longrightarrow \underset{\text{Complex}}{(\ddot{D} \longrightarrow A)} \xrightarrow{\text{Polar solvent}} \underset{\text{Radical anions}}{D^+ + A^-}$$

Scheme-I: Proposed mechanism of the reaction between domperidone and DDQ

$$DM + I_2 \longrightarrow DM\text{-}I_2 \text{ (Outer complex)}$$
$$DM - I_2 \longrightarrow [DM - I]^+ I^- \text{ (Inner Complex)}$$
$$[DM - I]^+ I^- + I_2 \longrightarrow [DM - I]^+ I^-_3$$
Tri-iodide ion pair complex

Scheme-II: Proposed mechanism of the reaction between domperidone and I_2

The absorptiometric properties of the coloured species as well as the influence of different parameters on the colour development are extensively studied to determine optimal conditions of the assay procedure. 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 reactions time. The low solubility of domperidone in most of the organic solvents restricted their use, although charge-transfer complexes are formed in those solvents. Acetonitrile was found to be an ideal solvent to carry out the reaction of domperidone with DDQ in method (**1**) 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 chloroform was found to be the best solvent to prepare domperidone and I_2 solutions in method (**2**) compared to many other solvents investigated.

The influence of concentration of DDQ and I_2 on the intensity of the colour developed at the selected wavelengths was studied. In method (**1**), the absorbance value was increased gradually with increasing the volume of 0.4 % DDQ reagent up to 2 mL, then from 2-6 mL the absorbance was unaffected. Hence, 2 mL of 0.4 % DDQ was used for the reaction in method (**1**). In method (**2**), the absorbance was found to increase with increasing concentration of I_2. 2 mL of 0.1 M I_2 gave maximum reading. Hence, based on the sensitivity with minimum blank absorbance, 2 mL of 0.1 M I_2 was fixed in method (**2**).

The optimum reaction time for the development of colour at ambient temperature (30 ± 2 ºC) was studied and it was found that complete colour development was instantaneous in method (**1**) and reaches completion after 20 min in method (**2**). The formed colour was stable for at least 0.5 h in both the cases. The molar ratio of domperidone to π- or σ-acceptors, DDQ or I_2 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 (DM:DDQ or I_2) complex.

Methods validation: Under the experimental conditions described, Beer's law is obeyed for both methods over the concentration ranges given in Table-1. Regression equations and correlation coefficients obtained by the method of least squares are also compiled in Table-1. The limits of detection and quantification were calculated from the standard deviation of the absorbance measurements from a series of ten blank solutions for each method. The limits of detection (K = 3) and limits of quantification (K = 10) were established according to IUPAC definitions[23] and recorded in Table-1.

In order to determine the accuracy and precision of the methods, pure drug solutions containing different concentrations of domperidone were prepared and analyzed applying the proposed procedure for each method. The analytical results obtained from this investigation are summarized in Table-2.

Applications: To ascertain the reliability of the methods, the proposed methods for the determination of domperidone were successfully applied to commercial tablets together with the reference method[24]. To avoid the interferences from additives and excipients usually found in formulations, the standard addition technique was adopted for both methods.

TABLE- 3
RESULTS OF DOMPERIDONE RECOVERY STUDY BY STANDARD-ADDITION METHOD

Formulation	DDQ method				I_2 method			
	Amount found (mg)	Pure added (µg/mL)	Pure found (µg/mL)	Pure recovered (%)*	Amount found (mg)	Pure added (µg/mL)	Pure found (µg/mL)	Pure recovered (%)*
Motilium tablets (10 mg/tablet) B. N. 02JB997	9.94	10	9.90	99.00	9.91	10	10.18	101.80
		20	20.30	101.50		20	20.27	101.35
		30	30.20	100.67		30	30.18	100.60
		40	39.60	99.00		40	40.36	100.90
		50	49.90	99.80		50	50.73	101.46
						60	60.54	100.90
Mean ± S.D.	99.99 ± 1.088				101.17 ± 0.444			

*Mean value of three determinations.

TABLE-2
STATISTICAL COMPARISON BETWEEN THE RESULTS OF THE PROPOSED METHODS FOR DETERMINATION OF DOMPERIDONE AND A REFERENCE

Value	DDQ	I_2	Ref. 30
Mean	100.4	100.7	100.4
±SD	0.767	0.709	0.707
n	7	7	6
Variance $(SD)^2$	0.588	0.503	0.499
t-test (2.201)*	0.2766	0.761	–
F-test (4.95)*	1.176	1.006	–

*Figures in parentheses are the theoretical *t*- and F-values at $p = 0.05$ confidence limit.

To a fixed amount drug in the formulation, pure drug was added at different levels and the total was found by the proposed methods. The experiment was repeated three times for each level. The results of this study presented in Table-3 reveal that accuracy and precision of the methods were unaffected by the various co-formulated substances. The results obtained were compared statistically by applying students t-test for accuracy and F-test for precision[25] with the reference spectrophotometric procedures. The results showed that the calculated t- and F- values were less than the tabulated values indicating that there was no significant difference between the proposed and the comparison methods.

Conclusion

The procedure employed for determination of domperidone is simple, precise, convenient, shorter reaction times, stable coloured species and inexpensive reagents. The determinations can be performed at room temperature and do not require heating step or pH adjustments. The proposed methods can be used as alternative methods to the reported ones for the routine determination of domperidone tablets. This encourages their successful use in routine analysis of this drug in quality control laboratories.

ACKNOWLEDGEMENTS

This project was supported by King Saud University, Deanship of Scientific Research, College of Science Research Center.

REFERENCES

1. J.S. Shindler, G.T. Finnerty, K. Towlson, A.L. Dolan, C.L. Davies and J.D. Parkes, *Br. J. Clin. Pharmacol.,* **18**, 959 (1984).
2. D. Silvers, M. Kipnes and V. Broadstone, *Clin. Ther*., **20**, 438 (1998).
3. The British Pharmacopoeia, The Stationary Office, London, p. 572 (2009).
4. M.S. El-Shahawi, S.O. Bahaffi and T. Ei-Mogy, *Anal. Bioanal. Chem*., **387**, 719 (2007).
5. T. Wahdan and N. Abd El-Ghany, *IL Farmaco*, **60**, 830 (2005).
6. K. Girish Kumar, P. Augustine and S. John, *J. Appl. Electrochem*., **40**, 65 (2010).
7. A.G. Seema, A.S. Atul, S.J. Yogini and J.S. Sanjay, *J. Planar Chromatogr.-Mod. TLC*, **19**, 302 (2006).
8. M. Veronique, S. Chantal and T. Jacques, *J. Chromatogr. B*, **852**, 611 (2007).
9. B. Patel, Z. Dedania, R. Dedania, C. Raolia, G. Vidya Sagar and R.S. Mehta, *Asian J. Res. Chem*., **2**, 210 (2009).
10. S. Thanikachalam, M. Rajappan and V. Kannappan, *Chromatographia*, **67**, 41 (2008).
11. A. Yadav, M.R. Singh, C. Satish, K.P. Saini and N.G. Singh, *J. Planar Chromatogr. Mod. TLC*, **22**, 421 (2009).
12. B.H. Patel, B.N. Suhagia, M.M. Patel and J.R. Patel, *J. Chromatogr. Sci*., **46**, 304 (2008).
13. D. Zhang, K. Chen, Y. Teng, J. Zhang, S. Liu, C. Wei, B. Wang, X. Liu, G. Yuan, R. Zhang and R. Guo, *Arzneimittelforschung*, **62**, 128 (2012).
14. D.H. Xu, H.G. Lou, H. Yuan, B. Jiang, Q. Zhou, Z.M. Zhang and Z.R. Ruan, *Biomed. Chromatogr*., **22**, 433 (2008).
15. M.I. Walash, F. Belal, N. Ei-Enany and A.A. Abdelal, *J. Fluoresc*., **18**, 61 (2008).
16. S.U. Kalure, R.B. Kulkarni and G.P. Somwanshi, *Der. Pharm. Chem*., **4**, 1517 (2012).
17. K. Kapil, S. Naik, J. Garima and N. Mishra, *Asian J. Res. Chem*., **2**, 112 (2009).
18. A.P. Sherje, A.V. Kasture, K.N. Gujar and P.G. Yeole, *Indian J. Pharm. Sci*., **70**, 102 (2008).
19. S.A. Amin and H.J. Ragab, *Anal. Sci*., **19**, 747 (2003).
20. O.Z. Devi, K. Basavaiah and K.B. Vinay, *Turk. J. Pharm. Sci*., **9**, 27 (2012).
21. E.A. Hissam, *J. Pharm. Biomed. Anal*., **17**, 1267 (1998).
22. I.M.Z. Sayed, *Cent. Eur. J. Chem.,* **7**, 870 (2009).
23. IUPAC, *Spectrochim. Acta B*, **33**, 241 (1978).
24. W. Baeyens and P. De-Moerloose, *Anal. Chim. Acta*, **110**, 216 (1979).
25. J.N. Miller and J.C. Miller, Statistics and Chemometrics for Analytical Chemistry, Pearson Education, edn. 4 (2000).