SENSITIVE AND SELECTIVE EXTRACTION FREE ION-PAIR COMPLEXOMETRIC DETERMINATION OF DOMPERIDONE IN PHARMACEUTICALS AND IN SPIKED HUMAN URINE

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ABSTRACT

Domperidone (DOM) is a drug used as an antiemetic and to control gastrointestinal effects of dopaminergic drugs in the management of perkinsonism. Two simple, rapid, sensitive and selective extraction free spectrophotometric methods have been developed for the assay of DOM in pure drug, in pharmaceuticals and in spiked human urine sample. The methods are based on the formation of yellow ion-pair complexes between DOM and two sulphonphthalein dyes viz., thymol blue (method A) and bromothymol blue (method B) in acetone and dichloromethane medium. The complexes showed absorption maxima at 390 nm and 410 nm in method A and method B, respectively. Reaction conditions were optimized to obtain the maximum color intensity. The absorbance was found to increase linearly with increase in concentration of DOM, which was corroborated by the calculated correlation values of 0.9991 in method A and 0.9986 in method B. The systems obeyed Beer's law over the concentration range of 1.25 - 20 $\mu\text{g mL}^{-1}$ in both the methods. The molar absorptivity values are calculated to be 1.53×10^4 and $2.06 \times 10^4 \text{ L mol}^{-1} \text{ cm}^{-1}$ for method A and method B, respectively and the corresponding Sandell sensitivity values are 0.028 and 0.021 $\mu\text{g cm}^{-2}$. The composition of the ion-pairs was found to be 1 : 1 by Job's method and the conditional stability constant (K_c) of the complexes have been calculated. The proposed methods were applied successfully to the determination of DOM in tablets as well as in spiked urine sample with good accuracy and precision.

Keywords: Domperidone, Assay, Spectrophotometry, Sulphonphthalein dyes, Pharmaceuticals, Spiked urine.

INTRODUCTION

Domperidone (DOM) is a D_2 -receptor antagonist used as an antiemetic. It is chemically known as 5-chloro-1-[1-[3-(2-oxo-2, 3-dihydro-1H-benzimidazole-1-yl)propyl]piperidin-4-yl]-1, 3-dihydro-2H-benzimidazol-2-one (Figure 1). It can be used in patients with Parkinson's disease¹ and is also found to be effective in the treatment of gastroparesis.² It is official in BP³ which recommends non-aqueous titration with perchloric acid as titrant and naphtholbenzein as indicator.

Fig. 1 Structure of Domperidone.

Literature survey revealed the availability of several methods for determination of domperidone in pharmaceutical formulations. Planar chromatography,⁴ high-performance liquid chromatography⁵⁻¹⁵ and high-performance thin-layer chromatography¹⁶⁻²⁰ have been used to assay DOM. The drug has also been assayed by differential pulse voltammetry²¹ and anodic difference pulse voltammetry²² at a glassy carbon electrode in Britton-Robinson buffer. Application of potentiometric sensors²³ for the analysis of DOM-containing tablets using PVC membrane and carbon paste sensors has also been reported. The most widely used technique for the assay of DOM has been UV spectrophotometry. Several UV-spectrophotometric²⁴⁻³⁶ procedures employing different media have been reported for assay in single as well as in combined dosage forms. There is only one report on the visible spectrophotometric assay of DOM in pharmaceuticals³⁷ in which four procedures are described. The first two methods are based on redox-complexation reactions involving Fe^{3+} , *o*-phenanthroline and bipyridyl³⁷ 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.³⁷ The

reported four visible spectrophotometric methods³⁷ involve a heating step and the procedures based on redox-complexation reactions require strict pH control. The reported chromatographic techniques 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. HPLC requires precolumn derivatization without preliminary separation. Voltammetric and potentiometric sensor methods currently available involve rigid pH control.

Several chromatographic techniques such as liquid chromatography-mass spectrometry,³⁸⁻⁴⁰ ultra performance liquid chromatography⁴¹ and high-performance liquid chromatography^{42, 43} have been reported for the determination of DOM in biological samples like human, dog and rat plasma. Many of these techniques are deficient in simplicity, cost-effectiveness and easy accessibility. No spectrophotometric method has ever been reported for assay of DOM in biological fluids. This prompted us to develop simple, sensitive and cost effective spectrophotometric methods for the assay of DOM in both pharmaceuticals and biological fluids.

In the present communication, the well-known ion-pair complex formation reaction has been employed for the determination of DOM in both pharmaceuticals and spiked human urine. The proposed methods have the advantages over the published methods in terms of simplicity, cost-effectiveness and freedom from cumbersome instrumentations.

EXPERIMENTAL

Apparatus

All absorbance measurements were made on a Systronics model 106 digital spectrophotometer (Ahmedabad, India) equipped with 1-cm matched quartz cells.

Materials and Reagents

All chemicals and reagents used were of analytical-reagent grade. The solvents used were of HPLC-grade.

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 200 $\mu\text{g mL}^{-1}$ DOM was prepared by dissolving 20 mg of pure drug in 2.5 mL methanol and diluting to 100 mL in a calibrated flask with acetone in method A or with dichloromethane in method B. The 200 $\mu\text{g mL}^{-1}$ DOM

solution was diluted to get 25 $\mu\text{g mL}^{-1}$ DOM with the respective solvents to use in method A and method B.

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.

0.05 % Thymol Blue (TB) and 0.1 % Bromothymol Blue (BTB)

The solutions were prepared by dissolving 0.050 g of thymol blue (Loba Chemie, Mumbai, India) in 100 mL of acetone (Merck, Mumbai, India) and 0.100 g of bromothymol blue (Loba Chemie, Mumbai, India) in 100 mL dichloromethane (Merck, Mumbai, India).

Construction of Calibration Curves

Method A

Aliquots of 0.25, 0.5, 1.0, 2.0, 3.0 and 4.0 mL DOM standard solution in acetone (25 $\mu\text{g mL}^{-1}$) were measured accurately and transferred into a series of 5 mL calibrated flask. To each flask, 1 mL of 0.05 % TB solution was added, diluted to the mark with acetone and mixed well. The absorbance of the resulting yellow color chromogen was measured at 390 nm against reagent blank.

Method B

Varying aliquots, 0.25, 0.5, 1.0, 2.0, 3.0 and 4.0 mL of 25 $\mu\text{g mL}^{-1}$ standard DOM solution in dichloromethane were measured accurately and transferred into a series of 5 mL calibrated flasks. To each flask was added 1 mL of 0.1% BTB. The content was mixed well and diluted to the mark with dichloromethane. The absorbance of each solution was measured at 410 nm against reagent blank.

In both methods, 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.

Procedure for Tablets

Ten tablets were accurately weighed and powdered. A portion equivalent to 10 mg DOM was accurately weighed and transferred into two 50 mL calibrated flasks, 2.5 mL of methanol and 30 mL of acetone or dichloromethane were added to the flasks and the content was shaken thoroughly for 15 - 20 min to extract the drug into the liquid phase; the volume was finally diluted to the mark with either acetone or dichloromethane (50 mL flask), mixed well and filtered using a Whatman No. 42 filter paper. An aliquot of the filtrate (200 $\mu\text{g mL}^{-1}$ in DOM) was further diluted to get 25 $\mu\text{g mL}^{-1}$ DOM with respective solvents and analyzed by following the procedures described for the calibration curve.

Analysis of Urine Samples

A 5 mL volume of DOM - free human urine taken into a 125 mL separating funnel was spiked with 5 mg DOM. One mL of 3 M NaOH was added, mixed and kept aside for 3 min. Then 30 mL of ethyl acetate was added, shaken well for about 15 min and collected the upper organic layer in a beaker containing anhydrous sodium sulphate. The water-free organic layer was transferred into a dry beaker and evaporated on a hot water bath. The dry residue was dissolved in 2.5 mL methanol and transferred into a 50 mL calibrated flask, and diluted to the mark with acetone or dichloromethane. The resulting solution equivalent to 100 $\mu\text{g mL}^{-1}$ DOM was further diluted to get 25 $\mu\text{g mL}^{-1}$ DOM with respective solvents and analyzed by following the procedures described for the calibration curve.

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 "Procedure of Tablets", and then subjected to analysis using the procedures described above.

Analysis of Synthetic Mixture

To the placebo blank of the composition described above, 10 mg of DOM was added and homogenized, transferred to a 50 mL calibrated flask and the solution was prepared as described under "Procedure of 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: 5.8698×10^{-5} M each of DOM and TB in acetone (method A) solutions; and 5.8698×10^{-5} M each of the DOM and BTB in dichloromethane (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) and completed as directed under the recommended procedures. The absorbance of the resultant ion-pair complex was measured at 390 nm and 410 nm in method A and method B, respectively.

RESULTS AND DISCUSSION

Spectrophotometric technique based on extraction-free ion-pair complex formation reaction has received considerable attention in the recent years for the quantitative determination of many pharmaceuticals.⁴⁴⁻⁴⁷ Since, DOM is an amino compound; attempts were made to determine it by applying ion-pair complex formation reaction. In the preliminary experiments, anionic dyes like TB and BTB were found to give yellow colored ion-pair complexes with positively charged drug; based on this observation two spectrophotometric methods have been developed using TB and BTB as chromogenic agents.

Absorption Spectra

Absorption spectra of the yellow colored ion-pair complexes DOM-TB and DOM-BTB are shown in Fig. 2 with absorption maxima at 390 and 410 nm, respectively. The developed yellow color is due to the conversion of the dye into an open quinoidal anionic derivative,^{48,49} which subsequently forms an ion pair with DOM as shown in Scheme 1.

Fig. 2 Absorption spectra (15 mg mL^{-1} DOM in method A and 10 mg mL^{-1} DOM in method B)

Optimization of Reaction Conditions

Optimum reaction conditions for quantitative determination of ion-pair complexes were established *via* various preliminary experiments such as choice of organic solvent, concentration of the dye and reaction time.

Choice of Organic Solvent

DOM is practically insoluble in most of the organic solvents except methanol. However in methanolic medium, even the reagent blank gave an intense yellow color. Hence, DOM was dissolved in minimum quantity of methanol and a number of organic solvents such as dichloromethane, acetone, dioxane and carbon tetrachloride were examined to carry out the experiments. In the case of method A, acetone was found as the ideal solvent, since high sensitivity with minimum blank absorbance was achieved in acetone medium whereas in method B, dichloromethane was selected as the suitable solvent, yielding maximum absorbance. The blanks yielded least absorption in these solvents.

Effect of Dye Concentration

The influence of the concentration of TB and BTB on the intensity of the color developed at the selected wavelength was studied. In method A, the blank absorbance was found to increase with increasing concentration of TB as shown in Fig. 3. One mL of 0.05% TB gave maximum absorbance with minimum blank reading (Fig. 3). Hence, based on the sensitivity with minimum blank absorbance, 1 mL of 0.05% TB was used. In method B, constant absorbance readings were obtained when (0.5 - 2.0) mL of 0.1% BTB was used (Fig. 3) and the respective blanks gave negligible absorbance values. Hence, 1 mL of 0.1% BTB was fixed in method B.

Fig. 3 Effect of dye (15 mg mL⁻¹ DOM in method A and 10 mg mL⁻¹ 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 the addition of the dye solutions resulted in an immediate full color development. The formed ion pairs were stable for at least 40 min in method A and 30 min in method B.

Composition of Ion-Pair Complexes

The composition of ion-pair complexes was established by Job's method of continuous variations using variable dye and DOM concentrations. In both methods, the results indicated that 1: 1 (DOM:Dye) ion-pair complex is formed through the electrostatic attraction between the positively protonated drug and the anion of dye (Fig. 4). Based on these findings, we propose a probable reaction mechanism for the formation of the complex as shown in Scheme 1.

Fig. 4 Job's Continuous - variations plots (a) method A and (b) method B

Scheme 1. The probable reaction mechanism

Conditional Stability Constants (K_f) of the Ion-Pair Complexes

The conditional stability constants (K_f) of the ion-pair complexes for DOM were calculated from the continuous variation data using the following equation:⁵⁰

$$K_f = \frac{A/A_m}{[1-A/A_m]^{n+2} C_M(n)^n}$$

where A and A_m are the observed maximum absorbance and the absorbance value when all the drug present is associated, respectively. C_M is the mole concentration of drug at the maximum absorbance and n is the stoichiometry with which dye ion associates with drug. The log $K_f \pm CL$ (Confidence limit at 95 %, $n = 3$) values for DOM - TB and DOM - BTB ion-pair associates were 6.457 ± 0.672 and 6.724 ± 0.561 , respectively.

Method Validation

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 1.25 - 20 µg mL⁻¹ in both methods (Fig. 5).

Fig. 5 Calibration curves; a. method A and b. method B.

The calibration graph in each instance is described by the equation:

$$Y = a + bX$$

(Where Y = absorbance, a = intercept, b = slope and X = concentration in $\mu\text{g mL}^{-1}$) 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 guidelines⁵¹ are compiled in Table 1 speak of the excellent sensitivity of the proposed methods. LOD and LOQ were calculated according to the same guidelines using the formulae:

$$\text{LOD} = 3.3\sigma/s \text{ and } \text{LOQ} = 10\sigma/s$$

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	390	410
Linear range, $\mu\text{g mL}^{-1}$	1.25 - 20	1.25 - 20
Molar absorptivity(ϵ), $\text{L mol}^{-1} \text{ cm}^{-1}$	1.53×10^4	2.06×10^4
Sandell sensitivity*, $\mu\text{g cm}^{-2}$	0.028	0.021
Limit of detection (LOD), $\mu\text{g mL}^{-1}$	0.22	0.75
Limit of quantification (LOQ), $\mu\text{g mL}^{-1}$	0.66	2.27
Regression equation, Y**		
Intercept (a)	0.0016	0.0184
Slope (b)	0.035	0.044
Standard deviation of a (S_a)	0.0165	0.126
Standard deviation of b (S_b)	0.0009	0.0068
Regression coefficient (r)	0.9991	0.9986

*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. **Y=a + bX, Where Y is the

absorbance, X is concentration in $\mu\text{g mL}^{-1}$, 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, $\mu\text{g mL}^{-1}$	Intra-day accuracy and precision (n = 7)			Inter-day accuracy and precision (n = 7)		
		DOM found, $\mu\text{g mL}^{-1}$	%RE	%RSD	DOM found, $\mu\text{g mL}^{-1}$	%RE	%RSD
Method A (using TB)	10	10.07	0.78	1.32	9.88	1.20	2.05
	15	14.78	1.49	1.25	14.69	2.07	1.71
	20	19.63	1.85	1.37	19.57	2.15	2.14
Method B (using BTB)	10	10.26	2.60	1.46	9.72	2.80	1.53
	15	15.38	2.53	1.73	14.6	2.67	1.75
	20	19.47	2.65	1.92	19.46	2.71	2.13

RE: Relative error and RSD: Relative standard deviation.

Robustness and Ruggedness

Method robustness was tested by making small incremental change in concentration of TB in method A and BTB 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 Table. 3.

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

Method	DOM taken, $\mu\text{g mL}^{-1}$	Method robustness	Method ruggedness	
		Parameter altered		
		TB mL in method A or BTB mL in method B RSD, % (n = 3)	Inter-analysts' RSD, % (n = 4)	Inter-instruments' RSD, % (n = 3)
Method A (using TB)	10	1.67	1.21	2.16
	15	1.43	0.93	2.29
	20	1.37	1.01	2.32
Method B (using BTB)	10	1.73	1.07	2.29
	15	1.89	0.96	2.18
	20	1.51	0.99	2.35

*TB and BTB volumes used were 0.8, 1.0 and 1.2 mL in both methods.

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 methods, there was no interference by the inactive ingredients as indicated by the near blank absorbance.

A separate experiment was performed with the synthetic mixture. The analysis of synthetic mixture solution yielded percent recoveries which ranged of 103.5 - 105.7 with standard deviation of 1.37 - 1.97 in both methods. 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.

Table 4 Recovery of the drug from synthetic mixture.

Method	DOM in synthetic mixture taken, $\mu\text{g mL}^{-1}$	DOM recovered* (Percent $\pm$ SD)
Method A (using TB)	10	105.7 $\pm$ 1.37
	15	103.8 $\pm$ 1.97
	20	104.6 $\pm$ 1.41
Method B (using BTB)	10	103.5 $\pm$ 1.63
	15	105.2 $\pm$ 1.84
	20	104.2 $\pm$ 1.57
*Mean value of five determinations		

Application to Analysis of Spiked Urine Sample and Tablets

The proposed methods were successfully applied to the determination of DOM in spiked urine sample with mean percent recovery $\pm$ S. D. in the range of 106.5 - 109.2 ($n = 5$) $\pm$ 1.68 - 2.09 in both methods (Table 5). In order to evaluate the analytical applicability of the proposed methods to the quantification of DOM in commercial tablets, the results obtained by the proposed methods were compared to those of the reference method³ 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 6) 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 Recovery of the drug from spiked human urine.

Method	DOM in spiked human urine taken, $\mu\text{g mL}^{-1}$	DOM recovered* (Percent $\pm$ SD)
Method A (using TB)	10	106.5 $\pm$ 1.91
	15	108.2 $\pm$ 1.68
	20	107.5 $\pm$ 2.09
Method B (using BTB)	10	108.7 $\pm$ 1.72
	15	109.2 $\pm$ 1.68
	20	106.9 $\pm$ 1.98
*Mean value of five determinations		

Table 6 Results of analysis of tablets by the proposed methods.

Tablet Brand name	Label claim, mg/tablet	Found* (Percent of label claim $\pm$ SD) (n=5)		
		Reference method	Method A (using TB)	Method B (using BTB)
Domstal-10**	10	98.47 $\pm$ 1.54	96.44 $\pm$ 1.72 t = 1.97 F = 1.25	97.52 $\pm$ 1.43 t = 1.01 F = 1.16
Vemistop-10***	10	101.25 $\pm$ 1.52	100.07 $\pm$ 1.74 t = 1.14 F = 1.31	102.3 $\pm$ 1.68 t = 1.04 F = 1.22

*Mean value of five determinations.

Torrent Pharmaceuticals Ltd., M. P, India; *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-analyzed 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 methods, the added DOM recovery percentage values ranged of 99.6 - 108.8 % with standard deviation of 1.41 - 1.98 (Table 7) indicating that the recovery was good, and that the co-formulated substance did not interfere in the determination.

Table 7 Accuracy assessment by recovery experiment.

Method	Tablet studied	DOM in tablet, $\mu\text{g mL}^{-1}$	Pure DOM added, $\mu\text{g mL}^{-1}$	Total found, $\mu\text{g mL}^{-1}$	Pure DOM recovered* Percent $\pm$ SD
Method A (using TB)	Vemistop -10	5.0	2.5	7.72	108.8 $\pm$ 1.41
		5.0	5.0	10.23	104.6 $\pm$ 1.67
		5.0	7.5	12.89	105.2 $\pm$ 1.96
Method B (using BTB)	Vemistop -10	5.11	2.5	7.60	99.6 $\pm$ 1.64
		5.11	5.0	10.44	106.6 $\pm$ 1.76
		5.11	7.5	13.22	108.1 $\pm$ 1.98
*Mean value of three measurements.					

CONCLUSIONS

The present communication reports the first spectrophotometric assay of DOM in biological fluid. The proposed methods are simple, rapid and selective compared to the published visible spectrophotometric methods of DOM in pharmaceuticals. The reported four visible spectrophotometric methods³⁷ of DOM 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 these methods,³⁷ the present methods can be applied at ambient temperature, color development is instantaneous and neither involves complicated extraction procedure nor requires strict pH control. Besides the simplicity and sensitivity of the procedures, the relative cheapness of apparatus and reagents demonstrate their advantageous characteristics. The methods are also useful due to high tolerance limit for common excipients found in drug formulations. These merits coupled with the use of simple and inexpensive instrument and high selectivity of the methods recommend the use of the methods in routine quality control Laboratories.

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