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Article

Validated UV Spectrophotometric Methods for the Simultaneous Estimation of Omeprazole and Domperidone

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ABSTRACT

A simple, precise, and accurate method is developed and validated for the simultaneous evaluation of Omeprazole (OME), Domperidone (DOM) in complex formulations (combined dosage form) using UV spectrophotometric methods. The method 1 developed is dual-wavelength method, measures the difference in the absorbance of the mixtures at wavelengths whereas single drug has the same absorbance and vice versa. Mean centered ratio method which depends on the construction of calibration by dividing spectra of the one compound with the other is reported as Method 2. The method 3 is derivative spectrum method, depends on zero-crossing points of the derivative spectrum, which enables the construction of calibration for the two drugs in the presence of second one. Simultaneous estimation of OME and DOM by the Q-absorption method and simultaneous equation method is already reported. To maintain the identical conditions throughout the experiment, the two methods Simultaneous equation method (Method 4) and the Q-Absorption method (Method 5) are repeated. All the five methods are tested for accuracy, precision by six replicate experiments and recovery studies using known synthetic mixtures. The calibrations are used for the analysis of two drugs in the tablet. The methods are validated in terms of ICH guidelines.

Key words: Omeprazole, Domperidone, Simultaneous equation, Q-Absorption, Derivative spectrum, Dual wavelength, Mean centered ratio method.

1. INTRODUCTION

1.1. Omeprazole (OME) Sodium

Omeprazole (OME) IUPAC name is 5-methoxy-2-{[(4-methoxy-3, 5-dimethyl-2- Pyridinyl) methyl] sulfinyl}-1H-benzimidazole. It acts as a proton pump inhibitor. It is used in the dyspepsia treatment and is used to treat peptic ulcers, laryngopharyngeal reflux, and syndrome and is used in cure gastroesophageal reflux disease. In peptic ulcers, by specific inhibition of the H+/K+-ATP as in the gastric cell, OME suppresses the secretion of gastric acid. OME blocks the acid production by acting on the proton pump, which reduces gastric acidity. UV spectrometry [1,2], visible spectrometry [3], TLC [4,5], and a variety of analytical techniques involving HPTLC [4], HPLC [6], electrochemical [7], and polarographic [8,9] techniques have been reported in the literature.

1.2. Domperidone (DOM)

DOM is an anti-sickness medicine. DOM IUPAC name is 5- chloro-1-{1-[3- (2, 3-dihydro-2-oxo-1H-benzimidazol-1-yl) propyl]-4- piperidinyl}-1, 3- dihydro-2H benzimidazol-2-one. It is an antiemetic used to relieve nausea and vomiting and promotes lactation in women. It also acts on the digestive tract and increases the movement of the intestines. It helps in the treatment of indigestion. It is a specific blocker of dopamine receptors. Literature survey revealed that UV [10-15], HPLC [16,17], RP-HPLC [18,19], and LC-MS [20] methods have been developed.

Literature survey shows that different methods such as UV Spectrophotometry [21,22], HPLC [23,24], RP-HPLC [25,26], and FT-IR [27] are developed in combined dosage forms. There are only two references available for simultaneous determination of dosage forms by UV spectroscopy using simultaneous equation and Q- Absorbance Ratio methods. However, there is no dual-wavelength, Mean centered ratio (MCR) spectra and derivative spectrum methods for the simultaneous estimation of OME and DOM in a combined formulation. Although methods such as dual wavelength method, derivative spectrum method, and MCR spectra offer sensitive, simple and accurate methods for simultaneous estimation of drugs. Simultaneous determination using the above methods has not reported yet. This prompted the authors to carry out the work in these lines. The successful results are obtained and communicated in this article. Structures of both the drugs were mentioned in Figure 1.

2. MATERIALS AND METHODS

2.1. Instrument Used

A double beam Elico UV-Visible spectrophotometer of model- SL 210 with a pair of 1cm matched quartz cells and UV-PC software 4.01.01 version was used.

2.2. Pure Samples

OME sodium and DOM were procured from Hetero drugs Pvt. Ltd. To prepare all the solutions, distilled water was used.

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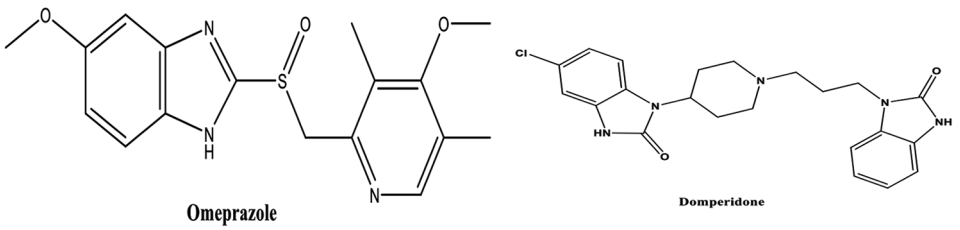

Figure 1: Structure of omeprazole and domperidone

2.3. Working Standard Solution Preparation

About 30 mg of OME and DOM were accurately weighed and shifted to 100 ml volumetric flask and dissolved in 50 ml of methanol and diluted with distilled water to get 300 µg mL^{-1} of OME and 300 µg mL^{-1} of DOM in separate volumetric flask. The standard stock solutions (300 µg mL^{-1}) were further diluted separately with 1:1 water and Methanol to get working standard of concentration 250 µg mL^{-1} of OME and 35 µg mL^{-1} of DOM.

λ max of the working standard solutions was determined by scanning the solutions in the entire UV range. The λ max of OME and DOM were observed at 301.2 nm and 287 nm.

2.4. Calibration Curves

Standard solutions of OME, whose concentration range is from 25 µg mL^{-1} to 250 µg mL^{-1} were added into the set of 10 mL standard flasks and standard solutions of DOM with a concentration range from 35 µg mL^{-1} to 350 µg mL^{-1} were taken into the set of 10 mL volumetric flasks. Then, 1:1 methanol and water were added to each flask to make the solution up to 10 mL. All the solutions scanned in the UV wavelength range from 200nm to 400nm. The absorbances versus the respective concentrations graphs were plotted to construct calibration curves. An overlain spectrum of OME and DOM in methanol is revealed in Figure 2.

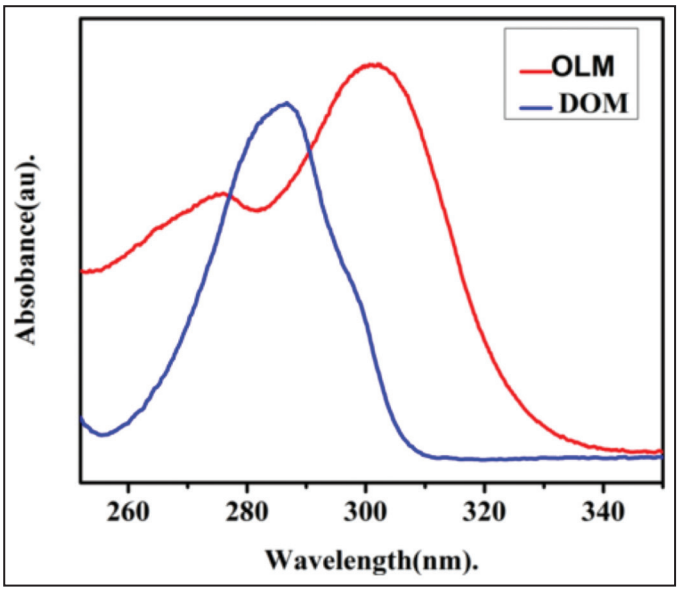

Figure 2: Overlain spectra of omeprazole and domperidone

2.5. Recommended Procedures

2.5.1. Method 1-Dual wavelength method

Different aliquots of 25–250 µg mL^{-1} and 35–350 µg mL^{-1} of OME and DOM were taken from their corresponding working standard solutions separately into two different sets of 10 mL standard flasks, then the volume was completed using 1:1 Methanol and distilled water. The aliquots were scanned in the wavelength between 200 nm and 300 nm in the UV spectrophotometer. Four wavelengths 274.8 nm, 290.0 nm, 294.8 nm, and 306.6 nm were selected from the overlain spectra (Figure 2), which are used for quantification of the two drugs using the Spectrophotometric double frequency technique. The quantitative assurance of OME is accomplished by estimating the absorbance distinction esteem between 274.8 nm and 294.8 nm whereas DOM shows equal absorbance values at the two wavelengths. The absorbance difference at 274.8 nm and 294.8 nm is directly proportional to the concentration of OME in the mixture. Quantitative measurements of the DOM are made by measuring the difference in absorbance values at 290 nm and 306.6 nm, whereas the OME shows the same absorbance values at both wavelengths. The difference in absorbance between 290 nm and 306.6 nm is relative to the concentration of DOM in the mixture. The OME and DOM calibration curve is created by plotting the difference in the absorbance value of a drug at a selected wavelength and its corresponding drug concentration. OME and DOM followed the Beer-Lambert law in the 2.5–25.0 µg mL^{-1} concentration ranges and 3.5-35.0 µg mL^{-1} for OME and DOM with good correlation coefficients.

2.5.2. Method 2-MCR method

Aliquots of OME corresponding to 2.5–25.0 µg mL^{-1} of their standard working solution were precisely transferred to a sequence of 10 ml volumetric standard flask and the limit was made sufficient with refined water. Record the absorption spectrum of the prepared solution between 200 and 300 nm which is divided by the standard spectrum of 24.5 µg mL^{-1} DOM, and concentrate the spectrum on the average ratio obtained. The spectra of DOM standard solutions with different concentrations in the range from 3.5 to 35.0 µg mL^{-1} were also measured. The recorded spectra were divided by the OME 12.5 µg mL^{-1} standard spectra to acquire ratio spectra and concentrated to the mean. The calibration curve of OME and DOM is plotted by taking the amplitude value of each center average spectrum (peak to peak) of each concentration.

2.5.3. Method 3- Derivative spectrum method

The derivative spectrum technique can be used to quantify analytes whose spectra overlap with minimal error, complicated extraction process since it can be quantified at the zero-crossing point of another drug; the interference from the second drug or additives in the formulation is small. Different aliquots equivalent to 25.0–250.0 µg mL^{-1} OME were taken into a set of 10mL standard flasks and 3.5–35.0 µg mL^{-1} of DOM were transferred to the above series and the capacity was made up to 10 mL using distilled water. Various 35.0–350.0 µg mL^{-1} aliquots of DOM were transferred separately to distinct series of 10 mL standard flasks and then 2.5–25.0 µg mL^{-1} OME were transferred to the above set of 10 mL standard flasks and bring the volume up to the mark using distilled water. Scan the solution in the wavelength range of 200 to 300 nm. Calculated the difference in O.D (Δ O.D) based on the data and constructed calibration curves by plotting the wavelength versus Δ O.D. Then, amplitude versus concentrations of the drug in the mixture graphs was constructed for both OME and DOM.

2.5.4. Method 4- Simultaneous equations method

For the formulation of simultaneous equations both wavelengths 301.2 nm which is the λmax of OME and 287 nm is the λ max of DOM were selected. Using a mixed standard solution OME showed linearity values in the range of 2.5–25 µg mL^{-1} and 3.5-35 µg mL^{-1} for DOM. The method is applicable for the sample containing two drugs, each drug of which absorbs at the λ max of the other drug. The constructed two equations depend upon the fact that the absorbance of a mixture of OME and DOM at 301.2 nm and 287 nm is the sum of the absorbances at their respective wavelengths. The absorptivity coefficients of the each drug were determined at two wavelengths. The concentrations of both the drugs present in the mixture were measured using the simultaneous equation with the formulae (1), (2).

$$\text{“}C_x = A_2ay_1 - A_1ay_2/ax_2ay_1 - ax_1ay_2 \quad (1)$$

$$C_y = A_1ax_2 - A_2ax_1/ax_2ay_1 - ax_1ay_2 \quad (2)\text{ ” [19]}$$

C_x is the concentration of OME in the working sample solution.
C_y is the concentration of DOM in the working sample solution (mixture).
A_1 = absorbance of mixture at 301.2 nm.
A_2 = absorbance of the mixture at 287 nm.
ax_1 = the absorptivity of OME at 301.2 and ax_2 = the absorptivity of OME at 287 nm.
(ax_1 =38.24, ax_2 =34.92).
ay_1 is the absorptivity of DOM at 301.2 nm and ay_2 are absorptivity of DOM at 287 nm.
(ay_1 =51.75, ay_2=62.11).

2.5.5. Method 5-Q-Absorption method

The Q-Absorption method (Isoabsorption method) deals with the ratio of the absorbance of the two selected wavelengths, in that one wavelength is the Isoabsorption point and the other is the λ max of one of the components**.** In the overlay spectra of both drugs, OME and DOM are known to exhibit iso-absorption points at 290.7 nm. The λ-max of OME, 301.2 nm is used as the second wavelength. Working standard solutions having concentration 2.5–25.0 µg mL^{-1} for OME and 3.5–35 µg mL^{-1} of DOM were set in 1:1 water and methanol, the absorbance values at 290.7 nm (Isoabsorption point) and 301.2 nm (λ max of OME) were measured and used the calibration curve to calculate absorption coefficients.

The concentration of both the drugs present in the solution of the mixture can be evaluated using the subsequent equations.

$$\text{“}C_X = [(QM - QY)/(QX - QY)] \times A_1/ax_1 \quad (3)$$

$$C_Y = [(QM - QX)/(QY - QX)] \times A_1/ay_1 \quad (4)\text{” [22]}$$

A_1 = the absorbance of the drug mixture at 290.7 nm
A_2 = the absorbance of the drug mixture at 301.2 nm;
$ax_{1=}$ the absorptivity of OME at 290.7 nm
ay_1 = the absorptivity of DOM at 290.7 nm
ax_2 = the absorptivity of OME at 301.2 nm
ay_2 = the absorptivity of DOM at 30.2 nm
$QM = A_2/A_1$
$QX = ax_2/ax$
$QY = ay_2/ay_1$.

Comparison of regression parameters of simultaneous equation method and Q-absorption method with reported parameters are given in Table 1.

Regression equation parameters of the other three methods are given in Table 2.

2.6. Analysis of Mixtures Prepared in the Laboratory

Recorded zero-order absorption spectra of various mixtures of OME and DOM manufactured in the laboratory in different proportions using distilled water as a blank. Then follow the procedure for each method under linearity. The concentration of OME and DOM in the prepared sample is measured from the calculated regression equation.

2.7. Analysis of the Drug Formulations

Weighed and crushed 10 OKACID D tablets (Cipla) to get a fine powder. Transferred powder tablets equivalent to approximately 60 mg OME and 30 mg DOM to a standard 100 ml flask and dissolved accurately in 20 ml

Table 1: Comparison of regression and analytical parameters of the proposed simultaneous equation method and Q-absorption method with reported one.

Parameters	Simultaneous equation method (proposed method)		Q-Absorption ratio method (proposed method)		Simultaneous equation method* (reported method)		Q-Absorption ratio method* (reported method)	
	OME	DOM	OME	DOM	OME	DOM	OME	DOM
Range	2.5–25 µg ml^{-1}	3.5–35 µg ml^{-1}	2.5–25 µg ml^{-1}	3.5–35 µg ml^{-1}	5–45 µg ml^{-1}	5–45 µg ml^{-1}	5–30 µg ml^{-1}	18–28 µg ml^{-1}
Slope	0.005	0.003	0.003	0.003	0.004	0.004	0.035	–0.026
Intercept	–0.095	0.059	0.066	0.074	0.2	0.04	0.0250	0.0225
Correlation co-efficient	0.996	0.989	0.993	0.990	0.9999	0.9996	0.999	0.998
Sandell's sensitivity (µg cm^{-2})	0.2	0.33	0.33	0.33	0.25	0.25	0.028	-0.38
LOD	1.386	1.54	4.598	0.77	1.15	0.66	0.4003	0.4448
LOQ	4.5	4.66	13.9	2.33	3.5	2.0	1.21	1.18
Accuracy (mean± SD)	100.01±1.17	100.1±1.23	99.98±0.99	98.99±0.86	100.05±1.14	98.89±1.15	99.8±0.03	98.8±0.45
Precision (Repeatability)	99.98±0.98	100.01±0.89	98.87±0.78	100.03±0.96	100.01±1.2	99.86±1.1	97.43±0.446	98.89±0.80

DOM: Domperidone, OME: Omeprazole

of methanol and sonicated the mixture for 35 min. Then bring the volume to 100 mL by using distilled water. After filtration of the solution through Whatmann filter paper, the resulting filtrate was appropriately diluted to acquire a concentration of approximately 60 µg mL^{-1} of OME and 30 µg mL^{-1} of DOM. The extinctions of the sample working solutions were recorded at 301.2 nm (OME λ max) and 287 nm (DOM λ max) and the concentrations of two active substances in the sample solution were determined with Eq. 1 and 2 (Method 4). The tablet solutions were subjected to analysis by the Q- absorption method. The absorbances of the sample solutions at 301.2 nm (OME λ max) and 290.7 nm (iso-absorbance point) and the concentration of both the drugs in the sample were recorded. They were determined by Equations 3 and 4 (Method 5).

The same solutions of tablet were used to plot the graphs in the OME and DOM dual-wavelength methods at 274.8, 294.8 nm (OME) and 290, 306.6 nm (DOM). The solutions are used for the calculations of the MCR method and the derivative spectrum method. Repeat the test procedure for the tablet formulation six times. The analysis of the tablet formulations results is shown in Table 3.

2.8. Recovery Studies

Studies of recovery were determined using the standard addition method in 3 different levels to study the accuracy of the mentioned methods. Known quantities of studied drugs were added to definite amount of pretested tablet powder and recovery percentages were calculated. The recovery studies were satisfactory which are given in Table 3.

3. RESULTS AND DISCUSSION

Therefore, The development of analytical methods are not only simple, precise, accurate but also fast and inexpensive, it is important in determining the investigational drugs, which is the main task of the developed spectrophotometry. UV spectrophotometry has the advantage of saving money and time when compared to HPLC technology, this work refers to the validation of five types of spectrophotometry, simultaneous equations, absorption ratio, derived spectrum, dual-wavelength, and methods which are simple, sensitive, accurate, and fast method for the simultaneous analysis of OME and DOM in their combined pharmaceutical dosage forms (Figures 3-10). Linearity for the five methods was observed in the range of 2.5–25 µg mL^{-1} for OME and 3.5–35 µg mL^{-1} for DOM. Analyzing the branded tablet, the quantity of drug estimated range of the proposed method is 99.73–100.21, as shown in Table 3.

Table 2: Regression and analytical parameters of the proposed dual-wavelength method, Mean centered ratio method, and derivative spectrum method for determination of OME sodium, DOM

Parameters	Dual wavelength method		Mean centered ratio method		Derivative spectrum method	
	OME	DOM	OME	DOM	OME	DOM
Range	2.5–25 µg ml^{-1}	3.5–35 µg ml^{-1}	2.5–25 µg ml^{-1}	3.5–35 µg ml^{-1}	2.5–25 µg ml^{-1}	3.5–35 µg ml^{-1}
Slope	0.031	0.027	0.155	0.311	0.002	0.003
Intercept	–0.072	0.043	–5.351	–3.469	–0.003	–0.0028
Correlation co-efficient	0.992	0.997	0.986	0.997	0.982	0.996
Sandell's sensitivity (µg cm^{-2})	0.032	0.037	0.006	0.0032	0.5	0.33
LOD	0.15	0.086	0.03	0.007	0.232	0.42
LOQ	0.456	0.259	0.091	0.022	0.705	0.129
Accuracy (mean±SD)	100.01±1.17	100.1±1.23	99.98±0.99	98.99±0.86	100.05±1.14	98.89±1.15
Precision (repeatability)	99.98±0.98	100.01±0.89	98.87±0.78	100.03±0.96	100.01±1.2	99.86±1.1

DOM: Domperidone, OME: Omeprazole

Table 3: Quantitative determination of OME and DOM in tablets by Simultaneous equation method, Q-absorption ratio method, dual-wavelength method, mean-centered ratio method, and derivative spectroscopy method and application of standard addition technique

Drugs parameters	Simultaneous equation method		Q-Absorbance ratio spectra		Dual wavelength method		Mean centered ratio method		Derivative spectrum method	
	OME	DOM	OME	DOM	OME	DOM	OME	DOM	OME	DOM
Taken µg mL^{-1}	4.75	7.0	4.75	7.0	4.75	7.0	4.75	7.0	4.75	7.0
	8.75	12.0	8.75	12.0	8.75	12.0	8.75	12.0	8.75	12.0
	12.5	18.0	12.5	18.0	12.5	18.0	12.5	18.0	12.5	18.0
Found µg mL^{-1}	4.74	6.99	4.76	7.01	4.76	7.0	4.74	7.01	4.76	6.98
	8.76	11.98	8.74	11.99	8.74	12.01	8.74	11.99	8.74	12.01
	12.49	18.01	12.5	17.99	12.49	18.01	12.51	18.01	12.51	18.01
%recovery	99.78	99.86	100.21	100.13	100.21	99.78	99.78	99.86	100.21	99.73
	100.01	99.83	99.88	99.91	100.11	99.88	99.88	99.91	99.81	100.08
	99.92	100.05	100.08	99.94	99.92	100.05	100.08	100.05	100.08	100.05
RSD	0.116	0.119	0.166	0.119	0.147	0.136	0.152	0.098	0.203	0.193

DOM: Domperidone, OME: Omeprazole

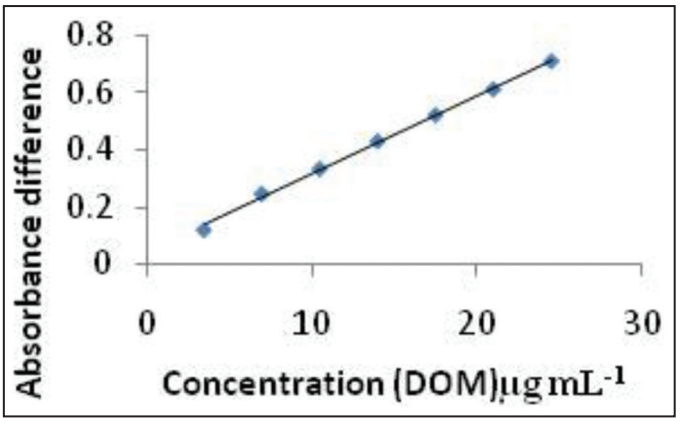

Figure 3: Dual wavelength of omeprazole

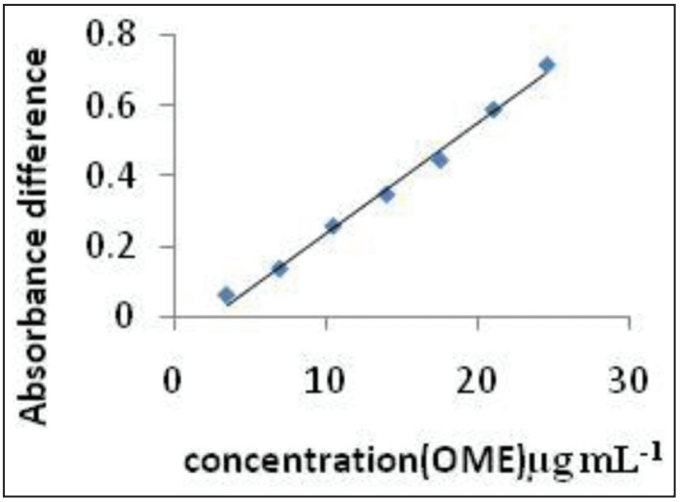

Figure 4: Dual wavelength of domperidone

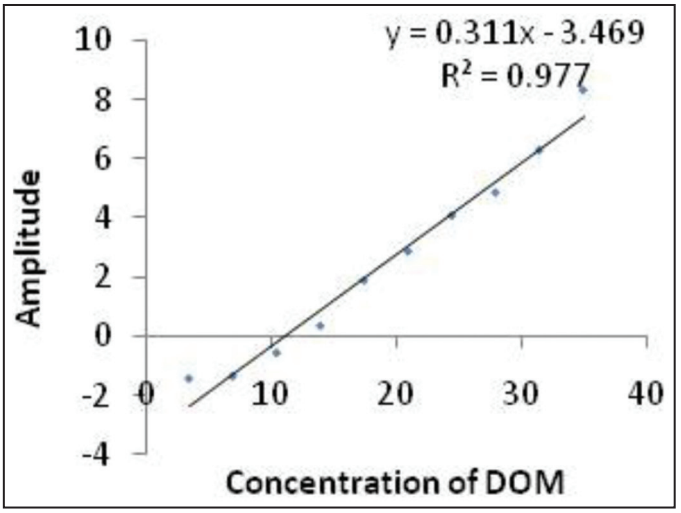

Figure 5: Mean centered ratio calibration curve for omeprazole

3.1. Method Validation

This method has been validated in accordance with the ICH recommendations.

3.2. Linearity

The linearity is related to proportionality to the concentration of the analyte in the samples. The calibration range for OME and DOM was determined taking into account the practical range required by the Lambert-Beer law, the concentrations of OME and DOM in the pharmaceutical dosage form to achieve accurate, precise, and linear results. The OME and DOM linearity ranges are listed in Tables 1 and 2.

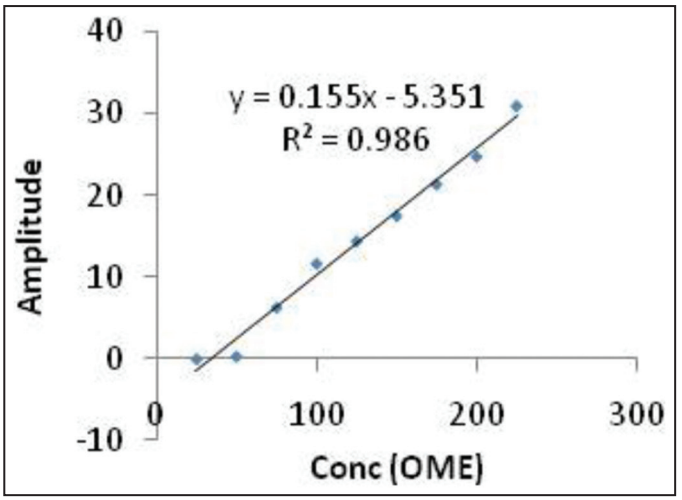

Figure 6: Mean centered ratio calibration curve for domperidone

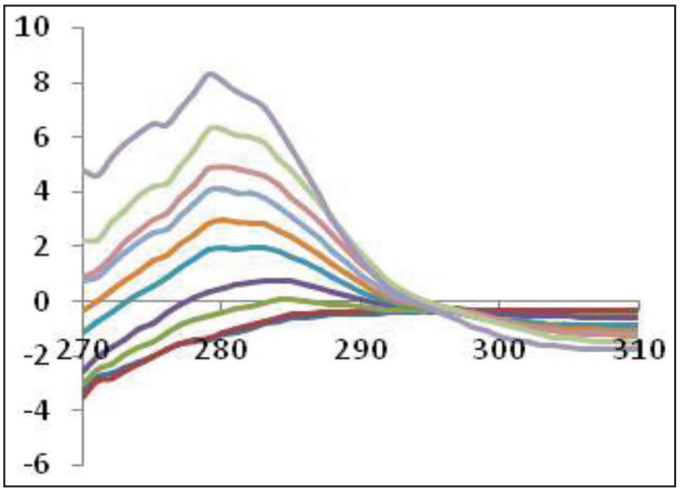

Figure 7: Mean centered ratio spectrum of omeprazole

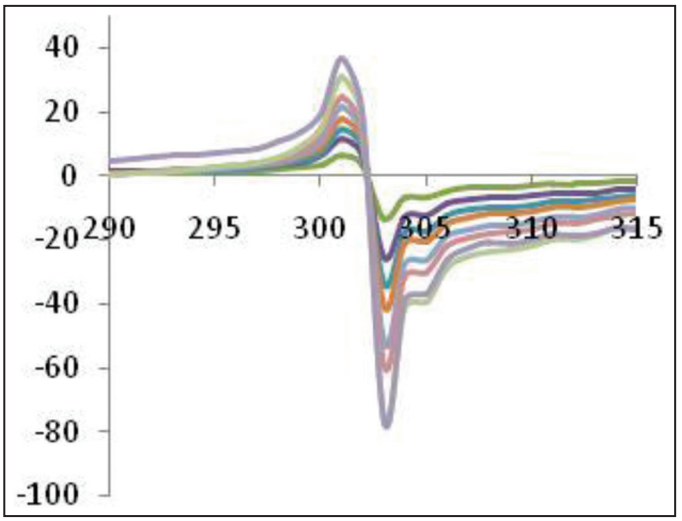

Figure 8: Mean centered ratio spectrum of domperidone

Table 4: Statistical analysis of the proposed Simultaneous equation method, Q-absorption ratio method, dual-wavelength method, MCR method, and Derivative spectrum method and reported one for determination of OME and DOM in their pure forms

Drugs parameters	Simultaneous equation method		Q-Absorbance ratio spectra		Dual wavelength method		Mean centered ratio method		Derivative spectrum method		Reported method	
	OME	DOM	OME	DOM	OME	DOM	OME	DOM	OME	DOM	OME	DOM
Mean%	99.91	99.98	100.19	100.01	100.02	99.98	99.74	99.95	99.84	100.02	99.8	99.9
SD	0.119	0.125	0.177	0.219	0.145	0.135	0.162	0.118	0.210	0.188	1.14	1.15
N	6	6	6	6	6	6	6	6	6	6	3	3
Student t-test	0.483	0.282	1.65	0.174	0.764	0.062	1.59	0.202	0.49	0.386	-	-
F-test	0.439	0.02	0.18	0.657	0.709	0.430	0.56	0.02	1.1	0.339	-	-

MCR: Mean centered ratio, DOM: Domperidone, OME: Omeprazole

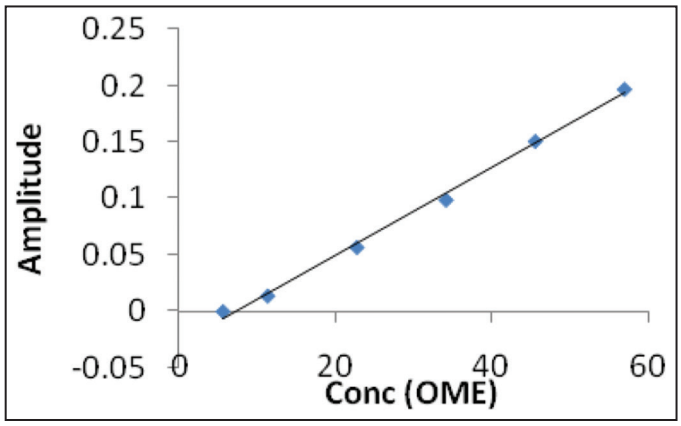

Figure 9: Calibration curve for derivative spectrum method for omeprazole

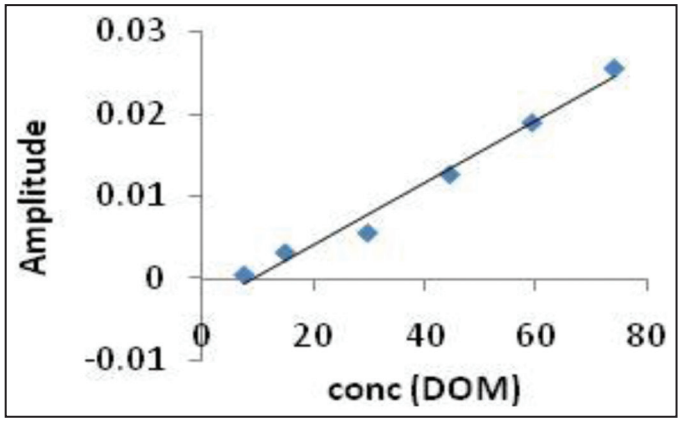

Figure 10: Calibration curve for derivative spectrum for domperidone

3.3. Precision

The precision is determined by analyzing a series of aliquots of a homogeneous sample which is able to calculate a valid estimate of the relative standard deviation in% (% RSD) statistically. Three replicates of (3.75, 6.25, 8.75 µg mL^{-1} OME and 5.25, 8.75, 12.25 µg mL^{-1} DOM) concentrations of the working standards of the mixture and the sample solution were analyzed and the relative standard deviation in% (% RSD) was found less than 2%.

3.4. Specificity

The results of the solution of corresponding tablet showed that noninterference from auxiliary substances compared to the standard working solution, therefore the method was designated as specific.

3.5. Limit of Detection

Limit of detection is the minimum amount of analyte in the sample which can be determined under specific experimental conditions. It is not necessarily quantified.

The LOD can be calculated using the following formula according to the ICH guidelines.

$LOD=3.3\times\sigma/S$

Here,

σ is the Standard deviation of the intercept; S is the Slope of the corresponding calibration curve.

3.6. Limit of Quantification

The limit of quantification is the minimum concentration of analyte in the sample which can be detected under established experimental conditions with acceptable precision and accuracy. The LOQ can be calculated by the following formula based on the ICH guidelines.

$LOQ=10\times\sigma/S$

Here, σ is the Standard deviation of the intercept; S is the Slope of the corresponding calibration curve. The values of Student's t-test and F-test are given in Table 4.

4. CONCLUSION

The suggested methods for the simultaneous determination of OME and DOM in pharmaceutical formulation proved to be simple, precise, accurate, inexpensive, and quick. It is found that in the developed method, % RSD is less than 2%. Therefore these methods may be used for the analysis of OME and DOM in combined formulations.

5. ACKNOWLEDGMENT

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