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A Redox Spectrophotometeric Method for the Determination of Some Anti-Ulcer Drugs

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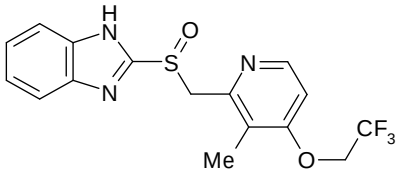
Summery A simple and sensitive derivative ratio spectrophotometric method is described for analysis of omeprazole (Ome), lansoprazole (Lan) and pantoprazole sodium (Pan). The method involves the reaction of these drugs with alkaline potassium permanganate, where a manganate ion is produced. The reaction is monitored spectrophotometrically by measuring the amplitude of the first derivative of the ratio spectra of reaction product at 584, 453 and 403 nm corresponding to zero crossing of the blank reagent. The calibration graphs were linear over the concentration range 11-110 μg ml^{-1}, 12.5–100 μg ml^{-1} and 13–130 μg ml^{-1} for Lan, Ome and Pan, respectively. The proposed method was applied successfully for the determination of these drugs in pure forms and in pharmaceutical dosage forms. The obtained results compared statistically with those of the official or reported methods for the analysis of these drugs, reveled high accuracy and good precision. The validity of the method was assessed according to USP guidelines and also by applying standard addition technique.

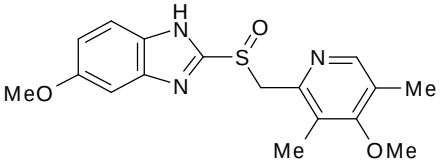
Introduction

The proton-pump inhibitors omeprazole, lansoprazole and pantoprazole inhibit gastric acid by blocking the H^+/K^+-adenosine triphosphatase enzyme system (the proton pump) of the gastric parietal cell[(1)]. They are α-pyridylmethylsulfinyl benzimidazoles with different substitutions on the pyridine or the benzimidazole groups, their pharmacological properties are similar[(2)]. Proton pump inhibitors are unstable at a low pH, therefore, the oral dosage forms are supplied as enteric-coated granules encapsulated in a gelatin shell (omeprazole and lansoprazole) or as enteric-coated tablets (pantoprazole).

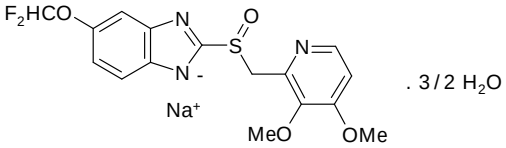
The granules dissolve only in alkaline pH, thus preventing degradation of the drug by acid in the oesophagus and stomach[2]. The structural formulae are shown as follows:



Lansoprazole



Omeprazole



Pantoprazole sodium sesquihydrate

Different analytical methods are reported in the literature for the assay of Lan Ome and Pan in dosage forms and in biological fluids including spectrophotometry [3-7]

,TLC[8], HPTLC[9-12], HPLC[13-18], and polarography[19-20].

Experimental

Instruments

Schimadzu 1601 UV recording spectrophotometer with two matched 1 cm quartz cells.

Samples

Pure samples

Lansoprazole working standard was kindly supplied by Sedico Pharmaceutical Co.6 October city, Egypt. The purity of the sample was labelled to be 100.98%, pantoprazole sodium sesquihydrate was supplied by Egyptian Pharmaceutical and Chemical Co., Ramadan City, Egypt and the purity of the sample was found to be 99.02%, omeprazole was supplied by Hetero Drugs limited. The purity of the sample was labeled to be 99.03%.

Market samples

Controloc® tablets (BYK) Konstanz, Germany B.N. 499871, labeled to contain 45.1 mg of pantoprazole sodium sesquihydrate equivalent to 40 mg of pantoprazole, Zollipak capsules; Manufactured by Sedico Pharmaceutical Co.6th October city, Egypt labeled to contain 15 mg of Lan B.N. 9101 (expired date 7/2002), Lopral capsules: supplied by T3A Co. Assuit, Egypt. B.N. 010639, labeled to contain 30 mg of Lan and Pepazole capsules: Manufactured by ALKAN Pharma B.N. 025 labeled to contain 40 mg omeprazole per capsule.

Chemicals and solvents

All chemicals used were of analytical grade and solvents were of spectroscopic grade. Potassium permanganate ($KMnO_4$), Merck, Germany, sodium hydroxide, El-Nasr Chemical Co., Cairo, Egypt.

Reagents

Potassium permanganate 3×10^{-3} M aqueous solution.

Sodium hydroxide solution (0.1 – 3 M) and Sodium hydroxide solution (0.01 M).

Standard solutions:

Lan stock standard solution: 44 mg in 100 ml of 0.01 M sodium hydroxide.

Ome stock standard solution: 50 mg in 100 ml of 0.01 M sodium hydroxide.

Pan stock standard solution: 65 mg in 100 ml of distilled water.

Procedure

Construction of calibration curve

Transfer 4.5 ml of 3×10^{-3} M $KMnO_4$ and 1.0 ml of 1 M sodium hydroxide solution into three series of 10-ml volumetric flasks. Add aliquots equivalent to 110-1100 μg of Lan (125-1000 μg of Ome, 130-1300 μg of Pan). Complete to volume with water and mix well. Measure the absorbance of Ome after 35 min (45 min for Lan & Pan) against a blank (1 ml 1 M sodium hydroxide and 9 ml of water), between 350 – 700 nm and the spectra were stored in the computer. The stored spectra of the reaction products of each drug were divided by the stored spectrum of the divisor (1.5 ml $KMnO_4$ + 1 ml of 1M NaOH completed to 10 ml with water).

The first derivative of the ratio spectra was obtained at 584, 453 and 403 nm, where the divisor is zero-crossing.

Calibration curves relating the amplitudes of ^{1}DD at 584, 453 and 403 nm and the corresponding concentration of each drug are plotted. The regression equations are computed.

Accuracy and precision

The previously mentioned procedures under linearity were repeated for the determination of (33, 44, 55, 66 and 99 μg of Lan) or (25, 50, 62.5, 75 and 90 μg of Ome) or (26, 52, 78, 91, 117 μg of Pan). The concentrations were calculated from the corresponding regression equations, at 584 nm and the mean percentage accuracy was calculated. Each concentration of Lan or Ome or Pan was analysed three times and the relative standard deviations were calculated.

Application of the proposed method for the determination of pharmaceutical formulations

Weigh accurately an amount of finely powdered and mixed content of ten capsules (or tablets after removing the colored coat with methanol and air dried) equivalent to 20.0 mg of Lan or Ome and 45 mg of Pan into a conical flask. Add 2 ml of 0.1 N sodium hydroxide, wait for 15 minutes. Add 100.0 ml of chloroform and stir with magnetic stirrer for 2 hours for Lan and Ome capsules or 4 hours for Pan tablet. Filter over 5 g of anhydrous sodium sulfate and evaporate chloroform. Add 50 ml of 0.01 M sodium hydroxide, stir for 10 minutes and filter. Transfer accurately 1 ml of each solution and proceed as mentioned under construction of calibration curve

Determine the concentration of each drug from its corresponding regression equation at 584 nm.

Results and Discussion

Potassium permanganate reagent was used for the determination of many pharmaceutical compounds in formulations and biological fluids, such as cefadroxil[21], chlorprothixene HCl[(22)], flupenthixol HCl[(23)], 5-alpha dihydrotesterone[(24)],organic

function group as aldehyde and ketone (benzaldehyde and benzophenone[25], triprolidine[26], tranmadol HCl[27] and nizatidine and ranitidine[28].

The reaction between Ome, Lan and Pan and $KMnO_4$ in alkaline medium yield a green color as a result of manganate species, which absorb at 610 and 435 nm. Zero-order absorption spectrum of reaction product and blank reagent (4.5 ml $KMnO_4$), Figure 1 shows severe interference, so it is difficult to measure absorbance directly at this wavelength. Thus, the first derivative of ratio spectra was useful for solving this problem using a blank reagent as divisor

Figure 2. Different parameters affecting the reaction product were studied.

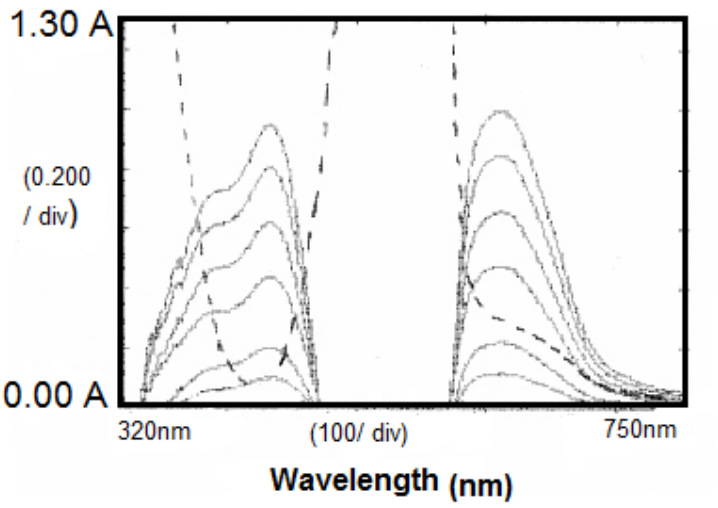


Figure 1: Zero-Order Absorption Spectrum of the Reaction Products of Pantoprazole Sodium (13 – 130 μgml^{-1}) with Potassium Permanganate (——), Blank (-----).

Effect of divisor concentration

The method was tested with various divisor concentration (1.5, 3 and 4.5 ml $KMnO_4$ 3 x 10^{-3} M), 1.5 ml $KMnO_4$ 3 x 10^{-3} M was chosen as the best divisor regarding sensitivity and repeatability.

The UV absorption spectrum of each reactant product is divided by the divisor and the first derivative was calculated for the obtained ratio spectra with $\Delta\lambda$ = 1.5 nm using

high smoothing to the curves. The amplitudes at 584, 453 and 403 nm are measured corresponding to zero crossing of the blank reagent.

Effect of sodium hydroxide concentration

One ml of different molarity of sodium hydroxide solution (0.1–3 M) is added to a fixed concentration of Lan, Ome or Pan. Measuring the absorbance of each one against its appropriate blank at 610 nm. One ml of 1 M NaOH was chosen.

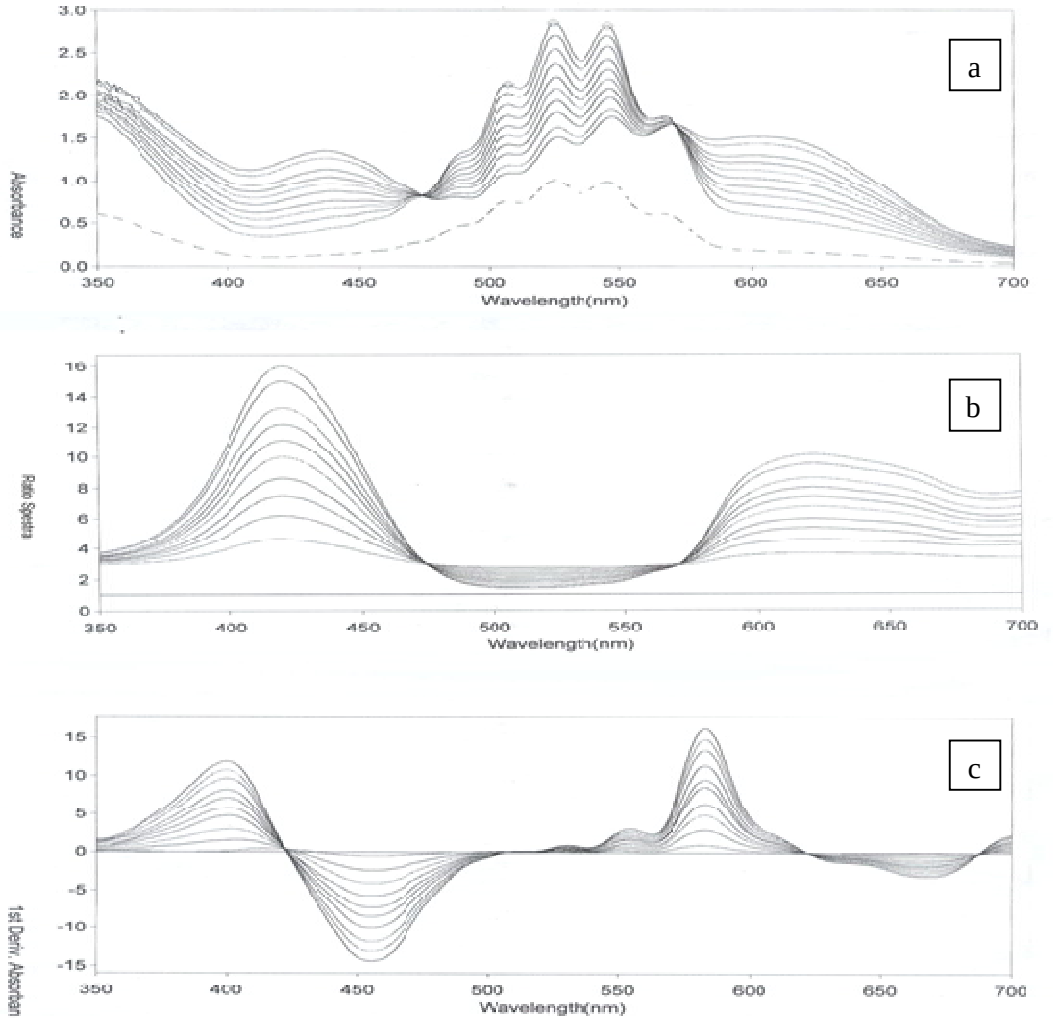


Figure 2: Zero-order Absorption Spectra (a), Ratio Spectra (b), First-Derivative of Ratio Spectra (c) of Lansoprazole (11-110 $\mu g ml^{-1}$) using 1.5 ml of $KMnO_4$ 3 x 10^{-3} M (-----).

Effect of $KMnO_4$ concentration

Different volumes of potassium permanganate 3 x 10^{-3} M were added to a fixed concentration of each drug. Measuring the absorbance of each against its appropriate blank, it was found that increasing the volume of $KMnO_4$ results in a subsequent increase in the absorbance up to 4.0 ml after which further increase in the volume produces constant absorbance values, thus, using 4.5 ml of $KMnO_4$ is appropriate for maximum absorbance measurement.

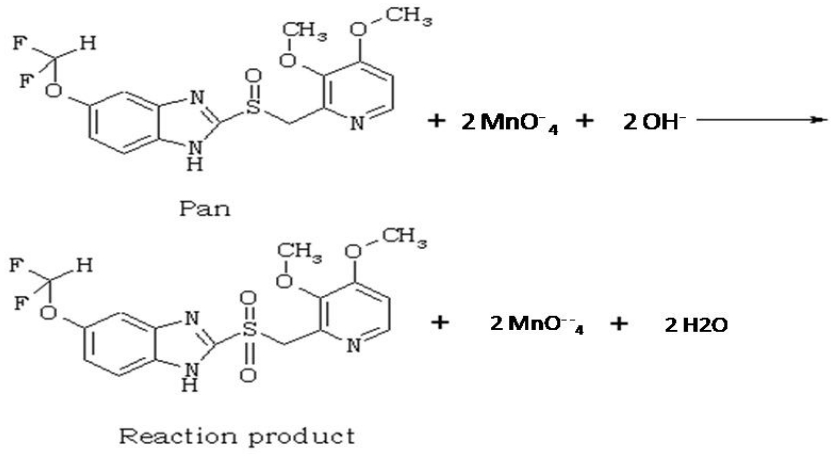
Effect of temperature

Heating the solution was found to increase the rate of the reaction but MnO_2 was precipitated. Therefore, room temperature was selected as the optimum temperature.

Under the above optimized conditions a linear correlation were obtained between the absorbance and concentration.

The calibration graphs were linear over the concentration range 11-110, 12.5 – 100 and 13 – 130 μg ml^{-1} for Lan, Ome and Pan, respectively,

The study of the continuous variation shows that the molar ratio of Drug: $KMnO_4$ is in a ratio of 1: 2, Figure 3, the suggested mechanism for the reaction with $KMnO_4$ is shown in the following scheme:



The proposed mechanism of the reaction between Pan and potassium permanganate in alkaline medium.

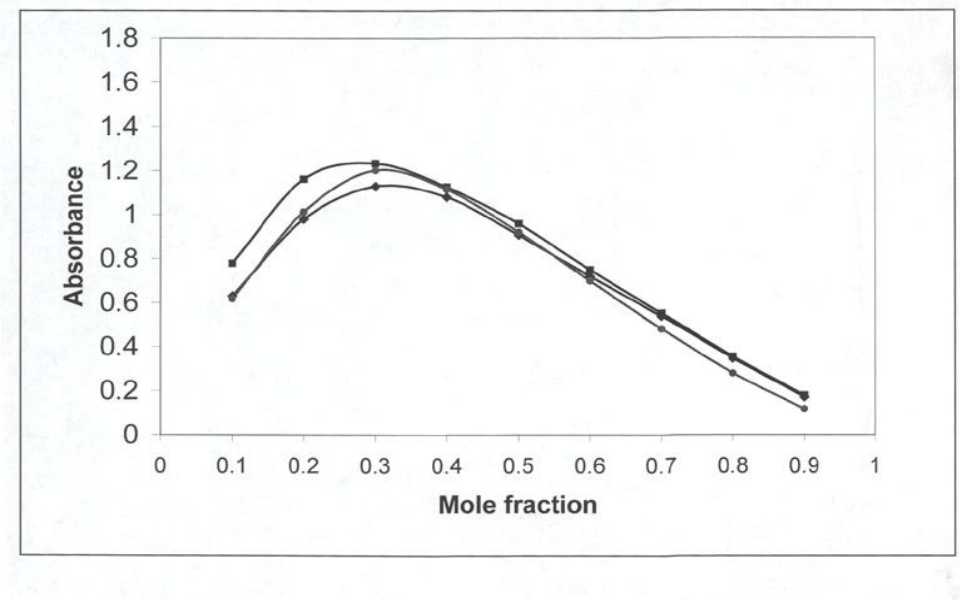


Figure 3: Stoichiometry of the Reaction of Lansoprazole (●—●), Omeprazole (■—■) and Pantoprazole Sodium (Δ—Δ) With Potassium Permanganate by Continuous Variation Method Using 3 x 10^{-3} M Solutions.

The proposed method was applied for the determination of Lan, Ome and Pan in pure powder form. Statistical analysis of the results obtained was compared with the reference methods for Lan[29]and Pan[30]or with the official method for Ome[31] using student's t-test and variance ratio F-test. The results revealed that no significant difference regarding accuracy and precision were found, Table 1. The method was successfully applied to determine each drug in its pharmaceutical formulations. The concentration of each drug was calculated using its corresponding regression equation and the results obtained were compared with the reference or official method, Table 1.

Table 1: Statistical analysis of the results obtained by the proposed [1]DD method and the reported methods for the determination of Lan & Ome and Pan in pure powder form and pharmaceutical formulations.

Values	*[1]DD method*	*Reported method*	*Preparation*	*[1]DD method at 584nm*	**Reported method**
1- For lansoprazole			**Lopral capsules [29] B.N. 010639**		
Mean	100.11	100.98		100.18	101.17
S.D.	1.37	0.55		1.52	0.67
n	5	3		5	3
Variance	1.88	0.30		2.31	0.45
T	1.26			1.27	(2.447)*
F	6.20			5.15	(19.300)*
2- For omeprazole			**Zollipak capsules[29] B.N. 9.01**		
Mean	99.53	99.02		212.35	78.45
S.D.	1.09	1.00		1.65	0.54
n	5	3		5	3
Variance	1.19	1.00		2.72	0.29
T	0.67				
F	1.19				
3- For pantoprazole			**Pepazol capsules[31] B.N. 025**		
Mean	100.14	99.03		99.10	99.82
S.D.	1.20	0.59		1.04	1.25
n	5	3		5	3
Variance	1.44	0.35		1.08	1.56
T	1.75			0.84	(2.447)*
F	4.14			1.44	(19.300)*
			Controloc tablets[30] B.N. 499871		
Mean				100.15	100.21
S.D.				0.95	0.68
n				5	3
Variance				0.90	0.46
T				0.10	(2.447)*
F				1.95	(19.300)*

The theoretical t = 2.447 and F = 19.300 value at P = 0.05

Also, the validity of the proposed method was checked by applying standard addition technique and those results are presented in Table 2.

Table 2: Results of the application of standard addition technique for the determination of Lan & Ome and Pan in pharmaceutical formulations by ^{1}DD method.

Preparation	*Claimed amount* ($\mu g ml^{-1}$)	*Standard added* ($\mu g ml^{-1}$)	**Recovery % of the added**
Lopral capsules	40	22	98.77
B.N. 010639	40	44	100.68
	40	66	100.05
Mean			99.83
S.D.			0.97
RSD.			0.97
Zollipak capsules	30	22	100.45
B.N. 9101	30	44	98.39
	30	66	99.33
Mean			99.39
S.D.			1.03
RSD.			1.04
Pepazol capsules	40	10	100.94
B.N. 025	40	50	99.38
	40	60	101.94
Mean			100.75
S.D.			1.29
RSD.			1.28
Controloc® tablets	45	13	98.77
B.N. 010639	45	39	101.13
	45	65	101.42
Mean			100.44
S.D.			1.45
RSD.			1.44

Results of assay validation are represented in Tables 3.

While, the proposed spectrophotometric method is not stability indicating, yet it has the advantage of simplicity, availability of the equipment and high sensitivity range as it determine Ome in the range of 12.5 – 100 μg ml^{-1} (The official method[32] is acid-base titration 1 ml of the titrant = 172.7 μg). Also, for Lan, Pan, the suggested method has the advantage of being low cost in comparison with the manufacture method (an HPLC method). Expired batches of Lan when determined by the proposed method gave high percentage recovery indicating presence of degradation products, Table 1.

Table 3 : Results of assay validation obtained by applying the proposed [1]DDmethod for the determination of Lan, Ome and Pan.

Parameters	*Lan*			*Ome*			*Pan*		
	584 nm	455 nm	400 nm	584 nm	455 nm	400 nm	584 nm	455 nm	400 nm
Linearity range ($\mu g ml^{-1}$)	11-110	11-110	11-110	12.5-100	12.5-100	12.5-100	13-130	13-130	13-130
Accuracy Mean ± RSD - Regression	100.11±1.37	99.01±0.81	100.29±1.19	99.53±1.10	100.49±1.43	101.18±0.95	100.14 ±1.20	101.15 ±0.84	100.16 ±1.31
Slope (b)	0.1527	0.16181	0.1175	0.1761	0.1707	0.1661	0.1586	0.1922	0.2010
SE of slope	0.00139	0.00183	0.00123	0.00111	0.00247	0.00169	0.00128	0.00156	0.00220
Intercept (a)	-0.2814	-1.24126	-0.8706	-0.49243	0.11343	-0.03096	0.044867	-0.97273	0.40407
SE of intercept	0.09516	0.12514	0.08421	0.06980	0.15597	0.10683	0.10356	0.12564	0.17760
Correlation coefficient	0.99985	0.99975	0.99979	0.99995	0.99975	0.99985	0.99985	0.99985	0.9995
SE of estimation	0.13929	0.18319	0.12327	0.08958	0.20016	0.13710	0.15160	0.18391	0.25998

Conclusion:

All statistical data proves validity of the proposed methods, which can be applied in industries for routine analysis of this method to analyze omeprazole, lansoprazole and pantoprazole in bulk drug and pharmaceutical preparation. These results indicate that the proposed method is sensitive, accurate, precise and reproducible.

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