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Spectrophotometric methods for the determination of lansoprazole and pantoprazole sodium sesquihydrate

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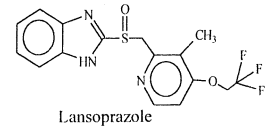
Abstract

Spectrophotometric procedures for determination of two irreversible proton pump inhibitors, lansoprazole (I) and pantoprazole sodium sesquihydrate (II) are presented. Two methods were based on charge transfer complexation reaction of these drugs, where they act as *n*-donors, with either π acceptor 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and with σ acceptor as iodine. A third method was also investigated depending on ternary complex formation with eosin and copper (II). The colored products were quantified spectrophotometrically using absorption bands at 457 nm for DDQ (method A) at 293 and 359 nm for iodine (method B) and at 549 nm using ternary complex formation (method C), for both drugs. The molar combining ratio and the optimum assay conditions were studied. These methods determined the lansoprazole in concentration ranges from 10 to 90, 1.48 to 6.65 and 3.69 to 16.61 μg ml^{-1} with mean percentage recovery 99.63% for DDQ, 99.71%, 99.18% for iodine and 99.76% for ternary complex and with relative standard deviation 0.11, 0.24, 0.13 and 0.36%, respectively. For pantoprazole, the concentration ranges were 10–60, 17.7–141.6 and 4.3–25.9 μg ml^{-1} with mean percentage recovery 99.51, 98.97, 99.84 and 99.46% and relative standard deviation 0.53, 1.21, 0.65, 0.81% for the three mentioned methods, respectively. Investigation of the formed complexes was made with respect to its composition, molar ratio of the reaction, association constant K_C^{AD}, molar absorptivity ε_λ^{AD} and free energy change ΔG for methods (A) and (B). The proposed methods have been applied successfully to the analysis of the cited drugs either in pure form or in pharmaceutical formulations, with good accuracy and precision, compared statistically with those given by the reported methods. They are recommended for quality control and routine analysis.

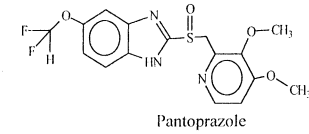
Keywords: Spectrophotometry; DDQ; Iodine; Ternary complex; Eosin; Copper (II); Lansoprazole; Pantoprazole

1. Introduction

Lansoprazole and pantoprazole sodium sesquihydrate are widely used as anti-ulcer drugs (proton pump inhibitors) through inhibition of H^+, K^+,-ATP-ase in gastric parietal cells. They reduce the gastric acid secretion regardless the nature of stimulation. The drugs are chemically known as 2-[(2-pyridylmethyl)-sulfinyl]-1H-benzimidazoles, the structural formulae are shown as follows:



Lansoprazole



Pantoprazole

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Several methods have been reported for determination of lansoprazole and pantoprazole in biological fluids and in pharmaceutical formulations including HPLC [1–9], TLC [10] HPTLC [11,12], capillary electrophoresis [13] and spectrophotometric determination [14].

A favorable characteristic of the proposed procedures is the speed, selectivity and ease of performing the assay. Scanning for the published methods for the determination of the cited drugs showed that the proposed methods have not been previously applied, consequently the present work describes a new colorimetric method which is less expensive than the published HPLC and capillary electrophoresis.

The methods depend on the reaction with π and σ acceptors DDQ and iodine with the cited drugs, also ternary complex formation with eosin and copper (II). Spectrophotometric determination of the reaction products was used to assay the drugs in pure and dosage forms.

2. Experimental

2.1. Apparatus

1. SHIMADZU 1601 PC UV VIS. Spectrophotometer, using quartz cell ($1 \times 1 \times 3$ cm) slit width 2 nm.
2. Digital pH meter, Pw 9409 Pye Unicam.

2.2. Material

2.2.1. Pure samples

Lansoprazole, working standard, kindly supplied by Pharco, Cairo, Egypt. The purity of the sample was found to be 99.42 ± 0.25 according to the reported method [15].

Pantoprazole sodium sesquihydrate (Byk Golden) Konstanz, Germany. The purity of the sample was found to be 98.79 ± 0.91 [16].

2.2.2. Market samples

Lazoral capsules (Pharco Pharmaceuticals), batch no. D110. Each capsule was labeled to contain 30.0 mg lansoprazole, 36.0 mg lactose, 100.0 mg maize starch, 10.0 mg carboxymethylcellulose calcium, 10.0 mg hydroxypropyl cellulose, 20.0 mg magnesium carbonate, 60.0 mg mannitol, 27.0 mg sucrose, 12.0 mg povidone, 40.0 mg hydroxyproyl methylcellulose phthalate and 4.5 mg cetyl alcohol.

Lanzor capsules (Roussel) batch no. 015. Each capsule was labeled to contain 30.0 mg lansoprazole, 11.2 mg magnesium carbonate, 55.0 mg neutral microgranules (38.5 mg saccharose and 16.5 mg corn starch), 29.9 mg saccharose, 18.2 mg corn starch, 20.0 mg low substitution hydroxypropyl cellulose, 0.7 mg hydroxypropyl cellulose, 22.3 mg eudragit L 30 D-55, 7.0 mg talc, 2.2 mg polyethyleneglycol 6000, 2.2 mg titanium dioxide, 1.0 mg polysorbate 80, 0.3 mg anhydrous colloidal silica.

Controloc® tablets (BYK) Konstanz Germany, batch no. 497261. Each tablet was labeled to contain 45.1 mg pantoprazole sodium sesquihydrate equivalent to 40.0 mg pantoprazole, 10.00 mg sodium carbonate, 42.70 mg mannitol, 50.00 mg crospovidone, 4.00 mg polyvidone k 90, 3.2 mg calcium stearate, 19.00 mg hydroxypropyl methylcellulose 2910, 0.38 mg polyvidone k 25, 0.34 mg titanium dioxide E 171/Cl 77891, 0.03 mg yellow ferric oxide E 172/Cl 77492, 4.25 mg propylene glycol, 14.56 mg eudragit L 30 D-55 (consisting of: 14.13 mg poly (ethylacrylate, methacrylic acid) 1:1 mw 250,000, 0.1 mg sodium lauryl sulfate, 0.33 mg polysorbate 80), 1.45 mg triethyl citrate, and 0.016 mg printing ink (opacode S-1-9210), dry residue.

2.2.3. Reagents and chemicals

All reagents and chemicals used were of analytical grade and were used without further purification. The solvents were of spectroscopic grade.

1. DDQ (Aldrich Co.), 0.4% w/v solution in acetonitrile, was freshly prepared (daily).
2. Iodine (BDH, Poole, UK), 5×10^{-3} M solution in chloroform, was stable for 1 week at 4°C
3. Eosin (Sigma), 2.0×10^{-3} M aqueous solution was stable for 2 weeks.

4. Copper sulphate. (Merck, 2.0×10^{-3} M aqueous solution, was stable for 2 weeks.
5. Methylcellulose (MC) (1500 CPS, Aldrich), 0.5% in cold water was stable for 2 weeks.
6. Buffer solution pH 4.5, prepared by mixing 0.2 M acetic acid solution and 0.2 M sodium acetate solution, the pH needed to be checked periodically.

2.2.4. Standard solutions

The standard solutions were stable for at least 1 week when preserved in a refrigerator except the aqueous solution of lansoprazole, which must be freshly prepared.

1. Lansoprazole (I), 2.707×10^{-3} M solution in acetonitrile for method (A).
2. Pantoprazole sodium sesquihydrate (II), 2.312×10^{-3} M solution in acetonitrile for method (A).
3. Lansoprazole (I), 10^{-3}M solution prepared by dissolving 36.94 mg in 100 ml chloroform, dilute this solution to 10^{-4} M with the same solvent for method (B).
4. Pantoprazole base (III), 10^{-3}M solution in chloroform for method (B). It was prepared as follows: an accurately weighed amount of pantoprazole sodium sesquihydrate equivalent to 38.34 mg base was transferred quantitatively into 125 ml separating funnel containing 10 ml 0.1 N sodium hydroxide. The solution was extracted with 4×20 ml chloroform. The extract was washed with 20 ml water filtered through anhydrous sodium sulphate into 100 ml volumetric flask and the volume was completed with chloroform to provide a standard of pantoprazole base of 10^{-3}M solution.
5. Lansoprazole (I), 10^{-3}M solution prepared by dissolving 36.94 mg in 2 ml methanol, and completed to 100 ml with distilled water. The solution must be freshly prepared for method (C)
6. Pantoprazole sodium sesquihydrate (II), 10^{-3}M solution, prepared by dissolving 43.24 in 2 ml methanol, and completed to 100 ml with distilled water in a volumetric flask for method (C).

2.3. Procedures

2.3.1. Construction of calibration curves

Calibration curves were constructed according to the optimum conditions mentioned in (Table 1).

2.3.1.1. DDQ [method (A)]. Different aliquots of each working standard solution were transferred into separate 10 ml volumetric flasks, 6 ml of DDQ reagent was added to each flask. The volume was completed using acetonitrile and the absorbance was measured against the reagent blank at 457 nm.

2.3.1.2. Iodine [method (B)]. Different aliquots of each working standard solution were transferred into separate 10 ml volumetric flasks, 2 ml of iodine solution was added to each flask. The volume was completed with chloroform and the absorbance was measured against the reagent blank after 5 min at 359 and 293 nm..

2.3.1.3. Ternary complex [method (C)]. Different aliquots of each working standard solution were transferred into separate 10 ml volumetric flasks. To each flask, 1.5 ml of 0.5% MC solution, 3 ml of acetate buffer (pH 4.5) and a total of 1.5 ml of each of 2.0×10^{-3} M copper (II) and 2.0×10^{-3} M eosin were added, respectively. The volume was completed with water, kept in a water bath at 60°C for 20 min and at 70°C for 25 min for lasoprazole and pantoprazole sodium sesquihydrate, respectively. The flasks were cooled to about 25°C for 5 min under tap water. The absorbance was measured at 549 nm for both drugs against a reagent blank.

2.3.2. Dosage forms

2.3.2.1. Lansoprazole. The contents of ten capsules of each of lazoral and lanzor capsules were emptied, weighed and powdered. An accurately weighed amount of the finely powdered contents equivalent to 100, 36.94 and 36.94 mg of lansoprazole were transferred to 100 ml volumetric flasks, shaken with 50 ml acetonitrile, chloroform, methanol-water for methods (A), (B) and (C),

Table 1
Optimum conditions used in the proposed methods

Parameters	Proposed methods					
	Lansoprazole			Pantoprazole sodium sesquihydrate (II)		Pantoprazole base (III)
	DDQ (A)	Iodine (B)	Ternary complex (C)	DDQ (II) (A)	Iodine (III) (B)	Ternary complex (II) (C)
Amount of standard taken (μg)	100–900	14.8–66.5	36.9–166.1	100–600	177–1416	43–259
Amount of reagent (ml)	6	2	–[a]	6	2	–[a]
Solvent used	Acetonitrile	Chloroform	Water	Acetonitrile	Chloroform	Water
Heating temperature	25°C	25°C for 5 min	Heat at 60°C for 20 min	25°C	25°C for 5 min	Heat at 70°C for 25 min
λ_{max}	457 nm	359 nm 293 nm	549 nm	457 nm	359 nm 293 nm	549 nm
Stability of coloured product (min)	20 min	40 min	120 min	20 min	40 min	120 min

[a] As mentioned in the text.

respectively, then made up to volume with the same solvent and filtered.

After preparation of the test solutions, proceed as described under construction of calibration curves.

2.3.2.2. Pantoprazole. Ten Controloc tablets were accurately weighed and ground into a fine powder. An accurately weighed amount of the powder equivalent to 100 mg for method (A) and 43.24 mg for method (C) of pantoprazole sodium sesquihydrate. For method (A) the powder was shaken in 50 ml of acetonitrile and made up to 100 ml by the same solvent. For method (C) the amount was shaken with 2 ml of methanol then with 48 ml water, then made up to 100 ml with water. Filtration followed in both cases. In method (B) a weighed amount of powder equivalent to 38.34 mg pantoprazole base was shaken with 10 ml 0.1 N NaOH and extracted with chloroform as in section 2.2.4.

After preparation of the test solutions as above, proceed as described under construction of calibration curves.

3. Results and discussion

The main purpose of this study was to establish simple spectrophotometric methods for the determination of the cited drugs in pure form and in their pharmaceutical dosage forms.

π and σ acceptors react with basic nitrogenous compounds as n-donors to form charge transfer complexes or radical anions according to the polarity of the solvent used [17]. Hence DDQ and iodine were used in the proposed methods for the determination of the cited drugs.

For DDQ method (A), the cited drugs acted as n-donors, they formed reddish brown product with DDQ which exhibited strong absorption maxima at 457, 547 and 588 nm (Fig. 1). These

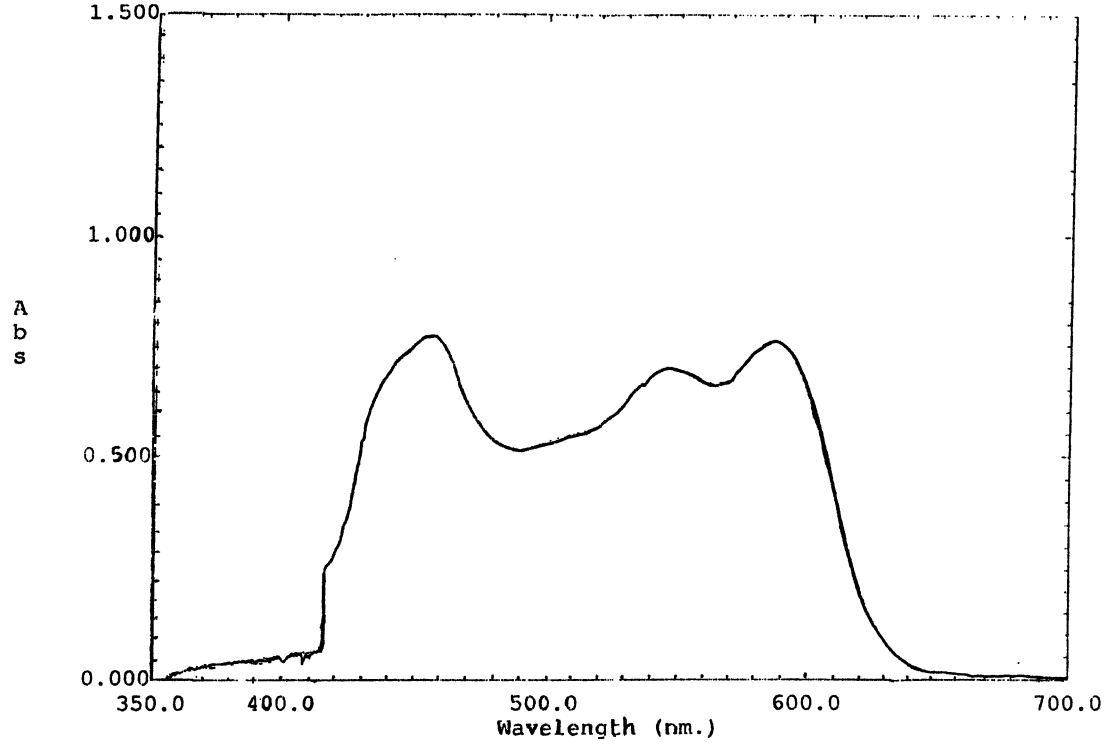


Fig. 1. Absorption spectrum of lansprazole–DDQ complex 70 μg ml^{-1}.

Table 2
Spectral data for the reaction of lansoprazole, pantoprazole sodium sesquihydrate (II) and pantoprazole base (III) with DDQ, iodine and ternary complex[c]

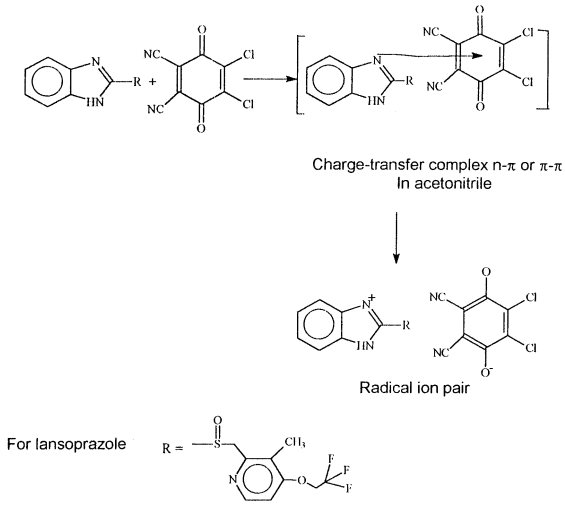
Parameters	Lansoprazole			Pantoprazole sodium sesquihydrate (II) pantoprazole base (III)		
	DDQ (A)	Iodine (B)	Ternary complex (C)	DDQ (II) (A)	Iodine (III) (B)	Ternary complex (II) (C)
Linearity range (μg ml^{-1})	10–90	1.48–6.65	3.69–16.61	10–60	17.70–141.60	4.30–25.90
Molar absorptivity	4.10×10^{3}	2.72×10^{4} [a] 5.65×10^{4} [b]	1.58×10^{4}	5.65×10^{3}	1.46×10^{3} [a] 2.44×10^{3} [b]	1.62×10^{4}
Intercept (a)	0.0089	0.0437[a] 0.0143[b]	0.0495	0.0833	0.036[a] 0.0455[b]	0.0702
R.S.D.% of intercept	0.99×10^{-4}	2.18×10^{-4} [a] 1.57×10^{-4} [b]	0.5×10^{-4}	2.24×10^{-4}	2.78×10^{-3} [a] 0.45×10^{-4} [b]	1.52×10^{-4}
Slope (b)	0.011	0.0673[a] 0.151[b]	0.0461	0.0146	0.0036[a] 0.0061[b]	0.0412
R.S.D.% of slope	1.96×10^{-4}	2.13×10^{-4} [a] 1×10^{-3} [b]	2.14×10^{-4} [b]	2.10×10^{-4}	2.55 x10^{-4} [a] 2.14×10^{-4} [b]	2.12×10^{-4}
Correlation coefficient (r)	0.9999	0.9994[a] 0.9992[b]	0.9995	0.9993	0.9995[a] 0.9996[b]	0.9998
Mean ± R.S.D.	99.63 ± 0.11	99.71 ± 0.24[a] 99.18 ± 0.13[b]	99.76 ± 0.36	99.51 ± 0.53	98.97 ± 1.21[a] 99.84 ± 0.65[b]	99.46 ± 0.81

[a] At λ_{359}.
[b] At λ_{293}.
[c] $A = a + bc$ (regression equation).

Table 3
Association constant K_C^{AD}, molar absorptivity values ε_λ^{AD} from Bensi-Hildebrand plots for the complex and the calculated free energy ΔG

Parameters	Lansoprazole	Pantoprazole
DDQ		
K_C^{AD}	5.914×10^2 l mol^{-1}	18.362×10^2 l mol^{-1}[a]
ε_λ^{AD}	25.862×10^2	8.189×10^2[a]
ΔG	−3.780 Kcal	−4.451 Kcal[a]
Iodine λ_{293}		
K_C^{AD}	137.057×10^2 l mol^{-1}	80.407×10^2 l mol^{-1}[b]
ε_λ^{AD}	37.924×10^2	2.934×10^2[b]
ΔG	−5.641 Kcal	−5.326 Kcal[b]

[a] Pantoprazole sodium sesquihydrate (II).
[b] Pantoprazole base (III).



Scheme 1.

bands may be attributed to the formation of DDQ radical anions, which are formed by complete transfer of n-electrons from donor to acceptor moiety in polar solvents. The reaction is represented by the following equation (and Scheme 1):

$$\underset{\text{Donor}}{D^{\cdot\cdot}} + \underset{\text{Acceptor}}{A} \rightarrow [D\rightarrow A] \rightarrow D^{\cdot+} + \underset{\text{Radical anion}}{A^{\cdot-}}$$

The stoichiometry of the reactions was studied by Job's method of continuous variation [18]. The molar ratio was found to be 1:1 (donor: acceptor) for both (I) and (II) with DDQ reagents.

The reaction conditions were optimized with regard to the volume of the reagent, nature of the solvent and effect of temperature as shown in (Table 1). Verification of Beer's law showed obedience in concentration ranges of 10–90 and 10–60 μg ml^{-1} with mean percentage recoveries of 99.63 and 99.51 and relative standard deviation of 0.11 and 0.53% for (I) and (II), respectively as shown in (Table 5).

Also the presented data (Table 2) illustrated the sensitivity ranges, molar absorptivity, regression equations, correlation coefficient and mean percentage recovery for the methods and R.S.D.% of the intercept and slope.

The absorbances of (I) and (II) were used to calculate the association constant using the Benesi–Hildebrand equation [19] which depends on the experimental condition that one of the two component species should be present in large excess, so that its concentration is virtually unaltered upon formation of the complex

$$\frac{[A_o]}{A_\lambda^{AD}} = \frac{1}{\varepsilon_\lambda^{AD}} + \frac{1}{K_C^{AD}\varepsilon_\lambda^{AD}}\frac{1}{[D_o]}.$$

Where $[A_o]$ and $[D_o]$ are the total concentrations of the interacting species, $A_\lambda^{AD}$and ε_λ^{AD} are the absorbance and molar absorptivity of the complex at the specified λ_{max}, and K_C^{AD} is the association constant of the complex. Upon applying the equation on the studied drugs a linear relation was obtained by plotting the values of $[A_o]/A_\lambda^{AD}$ versus $1/[D_o]$ which was given by the following equations.

$$[A_o]/A_\lambda^{AD} = 0.387\times10^{-3} + 6.54\times10^{-7}\ 1/[D_o] \text{ for lansoprazole (I)} \quad (1)$$

$$[A_o]/A_\lambda^{AD} = 1.221\times10^{-3} + 6.65\times10^{-7}\ 1/[D_o] \text{ for pantoprazole sodium sesquihydrate (II)} \quad (2)$$

From Eqs. (1) and (2), the association constant K_C^{AD}, and the molar absorptivity ε_λ^{AD} were calculated. The free energy ΔG for the cited drugs was

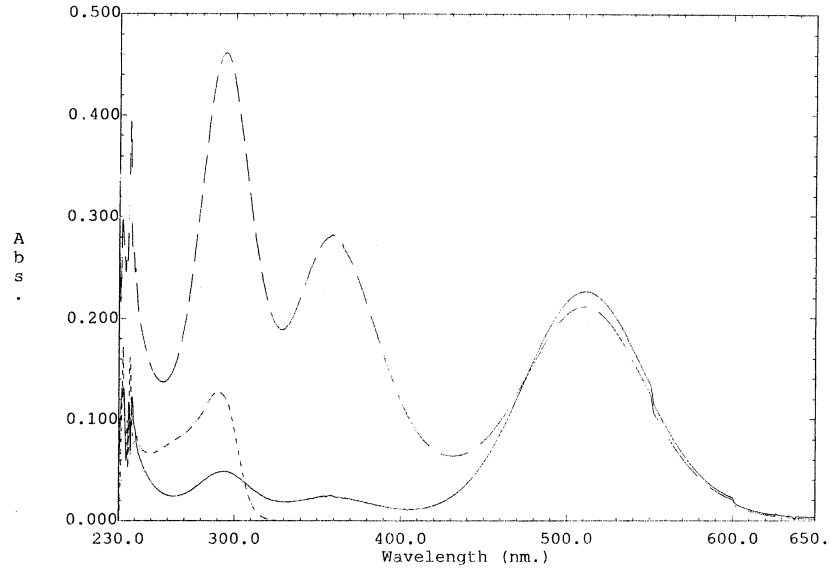


Fig. 2. Absorption spectra of pantoprazole base 70.8 μg ml^{-1} (…); iodine 10^{-3} M (—) and their reaction product in chloroform (---).

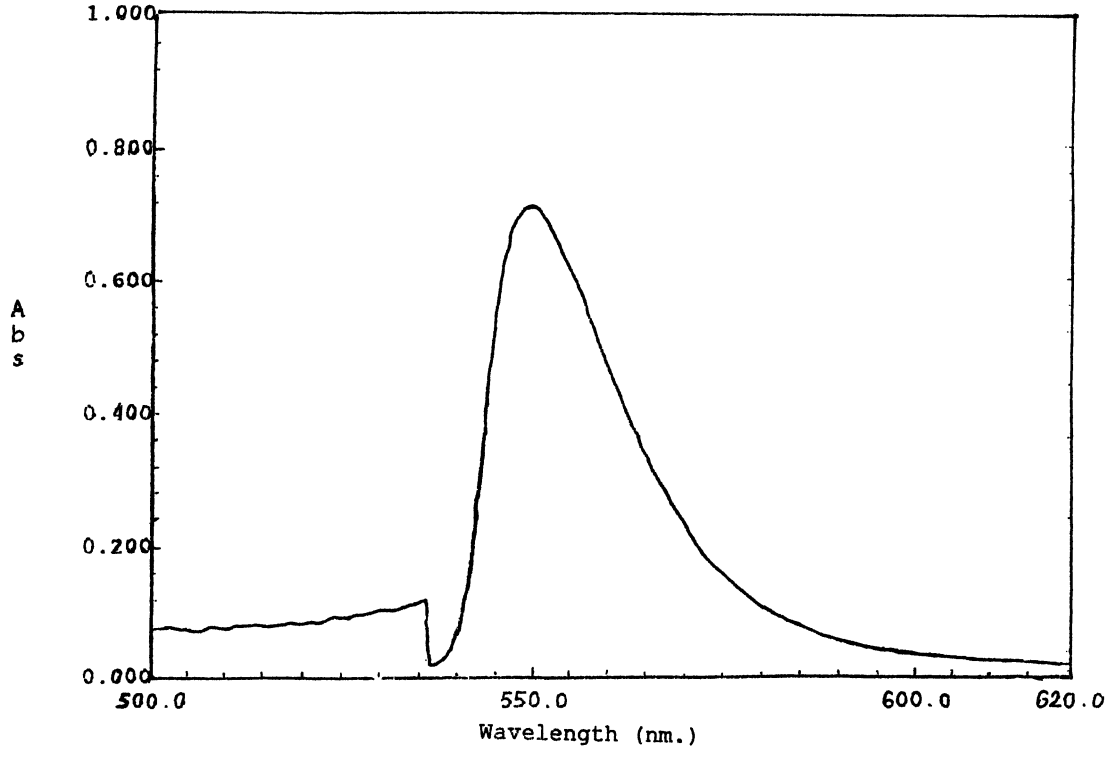


Fig. 3. Absorption spectrum of the ternary complex of lansoprazole (16.61 μg ml^{-1}) with eosin and Cu (II).

also calculated using Arrhenius equation [20,21].The values are shown in (Table 3).

For iodine [method (B)]: iodine in chloroformic solution displayed an absorption peak at about 520 nm, while the cited drugs showed a negligible absorption in the 320–650 nm region. Mixing the chloroform extract of lansoprazole (I) or pantoprazole base (III) with the iodine solution in chloroform resulted in a change of the absorption band of the iodine which exhibited hypsochromic shift. The charge-transfer complex between the cited drugs and iodine exhibited two absorption bands at 293 and 359 nm for both drugs as shown in Figs. 2 and 3. As described in the literature [22] the formation of triiode ion pair, which is the measurable species, was due to the transformation of an 'outer complex' to an 'inner complex' liberating I^- ions which react with the free molecular iodine. In other words, the interaction between (I) and (III) and iodine is a charge-transfer complexation reaction between the *n*-donor (benzimidazole ring) and the σ-acceptor iodine followed by the formation of a radical ion according to the following scheme:

$$R + I_2 \ldots R - I_2 \text{ (outer complex)}$$

$$R - I_2 \ldots [R - I]^+ \; I^- \text{ (inner complex)}$$

$$[R - I]^+ \; I^- + I_2 \ldots [R - I]^+ \; I_3^- \text{ (triiode ion pair)}$$

Where R = drug.

Regarding the third step in the above scheme, iodine alone did not absorb at the wavelength of maximum absorption, hence the stoichiometry showed only the iodine ion released in the second step as a result of one mole of iodine being consumed in the third step [23]. This was postulated on the basis of the molar ratio of the cited drugs to iodine (1:1) by application of Job's method and consideration of previous reports [24] on similar reactions. The optimum conditions of the reaction between iodine and the cited drugs were carefully studied and the results are presented in (Table 1).

Beer's law was obeyed in concentration range from 1.48 to 6.65 μg ml^{-1} for lansoprazole (I) at λ_{359} and λ_{293} with mean percentage recoveries of 99.71, 99.18% and relative standard deviation of 0.24, 0.13, respectively. In case of pantoprazole base (III) the concentration range was 17.70–141.60 μg ml^{-1} at λ_{359} and λ_{293} with mean percentage recoveries of 98.97, 99.84% and relative standard deviation of 1.21, 0.65, respectively.

(Table 2) Illustrates sensitivity ranges, molar absorptivity, regression equations, correlation coefficients and mean percentage recovery for the method. In this case, the decreased ability ofpantoprazole base (III) to form complex with iodine in chloroform solutions compared to lansoprazole, may be attributed to the powerful electron withdrawing effect of $-OCHF_2$ group in meta-position to the basic nitrogen of imidazole ring. In chloroform, the unshared electrons were not solvated and consequently may be affected by electronic effect.

The molar absorptivity and association constant for (I) and (III)-iodine reaction products were calculated using the Benesi–Hildebrand equation, according to the following equations:

$$[A_o]/A_\lambda^{AD} = -0.26 \times 10^{-3} + 1.29 \times 10^{-8} \; 1/[D_o] \text{ for lansoprazole (I)} \quad (3)$$

$$[A_o]/A_\lambda^{AD} = 3.408 \times 10^{-3} + 4.24 \times 10^{-7} \; 1/[D_o] \text{ for pantoprazole base (III)} \quad (4)$$

The calculated values are shown in (Table 3).

For ternary complex method (C): the main purpose of this study was to establish simple spectrophotometric method without prior extraction. The proposed method using ternary complex formation with eosin and Cu (II) was described. Ternary complex formed between the metal ion: electronegative ligand and organic base often have higher values of molar extinction coefficient than binary complexes of the same components. The formation of ternary complexes was reported to improve not only the sensitivity but also the selectivity as well. A typical feature is that in ternary complexes the third component could not weaken the bond between the first two, but sometimes it could even reinforce the stability of the complex [25].

Ternary complex formation had been used for determination of Pd (II) via 1,10 phenanthroline

Table 4
Recovery percentage for standard addition technique applied on dosage forms of lansoprazole and pantoprazol using the proposed and reported methods[a]

Preparations	Recovery % ± R.S.D.[d]			
	DDQ method (A)	Iodine method (B)	Ternary complex method (C)	Reported method
Lansoprazole				
Lanzor capsules 30 mg/capsule B.N. 015	99.52 ± 0.63 $F = 5.67$ (6.4) $t = 0.09$ (2.31)	98.95 ± 0.87[b] $F = 2.96$ (6.4) $t = 0.65$ (2.31) 99.21 ± 0.95[c] $F = 2.49$ (6.4) $t = 0.39$ (2.31)	99.24 ± 0.66 $F = 5.17$ (6.4) $t = 0.39$ (2.31)	99.61 ± 1.50
Lazoral capsules 30 mg/capsule B.N. D 110	100.24 ± 0.66 $F = 1.66$ (6.4) $t = 0.72$ (2.31)	99.69 ± 0.57[b] $F = 2.22$ (6.4) $t = 0.17$ (2.31) 99.78 ± 0.81[c] $F = 1.10$ (6.4) $t = 0.01$ (2.31)	99.83 ± 1.24 $F = 2.13$ (6.4) $t = 0.05$ (2.31)	99.79 ± 0.85
Pantoprazole				
Sodium sesquhydrate Controloc® tablets 45.1 mg/tablet B.N. 497261	98.63 ± 1.10 $F = 1.6$ (6.4) $t = 0.44$ (2.31)	99.25 ± 0.78[b] $F = 3.18$ (6.4) $t = 1.15$ (2.31) 99.42 ± 0.94[c] $F = 2.19$ (6.4) $t = 1.27$ (2.31)	98.79 ± 0.95 $F = 2.14$ (6.4) $t = 0.63$ (2.31)	98.18 ± 1.39

[a] Figures between brackets are the corresponding theoretical values.
[b] $\lambda_{359.}$
[c] $\lambda_{293.}$
[d] The average of five experiments.

as a cationic component and eosin as an anionic counter ion [26]. On the same basis, Fujita et al. [27] determined a group of drugs by formation of ternary complex with Pd (II) and eosin. In their studies nine cations have been tried, Pd (II) was proved to be the only effective metal ion.

In the present study, trials to use Pd (II), Pb (II) as complexing ion with the studied drugs were unsatisfactory. Among the studied metal ions, Cu (II) gave the highest sensitivity and reproducibility. Appropriate conditions were established for the color reaction and for the eosin: Cu (II): drug ratio to reach maximum sensitivity.

Color reactions of various drugs in aqueous media were investigated utilizing the ternary complex formation such as chlorpromazine, thiamine, lincomycin, ofloxacin and theophylline [27], ciprofloxacin and norfloxacin [28] and astemizole, terfenadine and flunarizine hydrochloride [29]. Scheme 2 was suggested for the formation of ternary compexes between the studied drug-metal ion [Cu (II) $(drug)_n$] as cation and (eosin) as anion, where structure (a) is more stable than (b), as a six membered ring is formed.

Optimum conditions for the reactions were established for the spectrophotometric determination of (I) and (II) by using eosin and Cu (II).

When the effect of pH on complex formation was studied, it was found that the optimum pH was in the range of 3.8–4.5, using 3 ml of the acetate buffer solution.

When a non-ionic surfactant methylcellulose

(MC) was used, prior extraction steps were unnecessary. The addition of surfactants to solubilize and stabilize the ternary complex had been previously reported [27]. Cationic surfactants such as cetylpyridinium chloride depressed the colored complex formation probably due to the formation of an ion-pair complex between eosin and the cationic surfactant. MC, which is a non ionic water-soluble polymeric surfactant, was reported to be the best dispersing agent with respect to sensitivity [27], accordingly, MC was used.

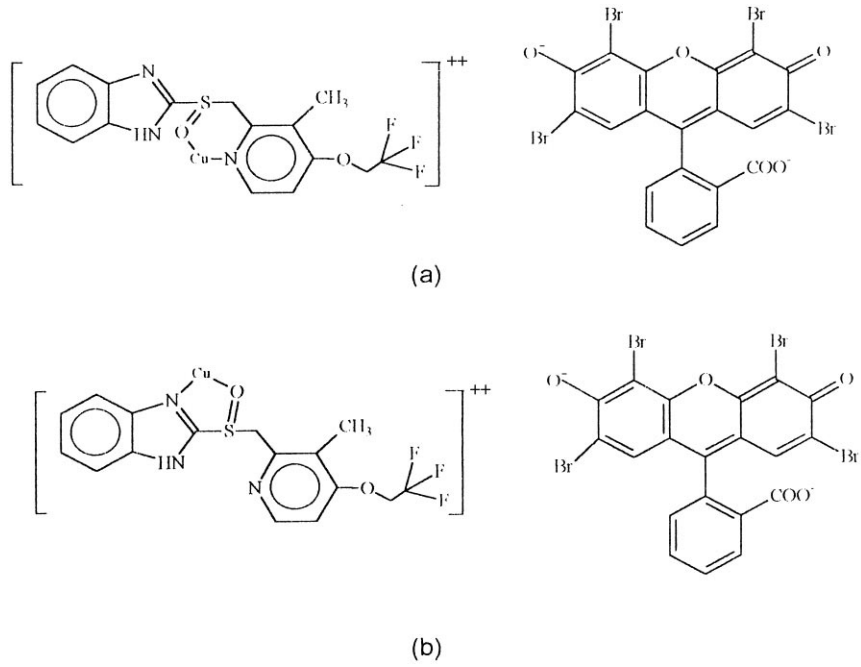
In this study, addition of MC was also found to be necessary for complex stability and prevention of precipitate formation. The acid dissociation properties of eosin in the presence of MC were determined spectrophotometrically at an ionic strength of 0.1 at 20 ± 0.1°C [30,31].

Depending on the pH of the solution, eosin can exist in any of the following forms:

$$H_3R^+ \overset{K_{a1}}{\rightleftharpoons} H_2R^+ \overset{K_{a2}}{\rightleftharpoons} HR^- \overset{K_{a3}}{\rightleftharpoons} R^{2-}$$

Where R denotes the anionic part of eosin. In this study, the pK_{a1}, pK_{a2}, pK_{a3}, in the presence of MC were 2.10, 2.85 and 4.95, respectively. At pH 4.3 about 80% of eosin was found to be in the form HR^- [32].

The effect of eosin and Cu (II) concentrations was examined by varying the molar ratio of eosin to Cu (II), while keeping the Cu (II): drug ratio constant. Maximum absorbance was observed



Scheme 2. Stable ternary complex, lansoprazole-Cu (II)-eosin. (a) Six membered complex is formed. (b) Five membered complex is formed.

Table 5
Statistical comparison between results of analysis of bulk powder of lansoprazole, pantoprazole sodium sesquihydrate (II) and pantoprazole base (III) applying the proposed and reported methods

	Lansoprazole				Pantoprazole			
	DDQ method (A)	Iodine method (B)	Ternary complex method (C)	Reported method [15][c]	DDQ method (A) (II)	Iodine method (B) (III)	Ternary complex method (C) (II)	Reported method [16][d]
Mean ± R.S.D.[a]	99.63 ± 0.11	99.71 ± 0.24 λ_{359} 99.18 ± 0.13 λ_{293}	99.76 ± 0.36	99.42 ± 0.25	99.51 ± 0.53	98.97 ± 1.21 λ_{359} 99.84 ± 0.65 λ_{293}	99.46 ± 0.81	98.79 ± 0.91
Variance	0.0121	0.0576 0.0169	0.1296	0.0625	0.2089	1.4641 0.4225	0.6561	0.8281
N	5	5	5	5	5	5	5	5
F	5.170 (6.4)[b]	1.090 (6.4) [b] 3.698 (6.4)[b]	2.074 (6.4)[b]		2.950 (6.4)[b]	1.768 (6.4)[b] 1.960 (6.4)[b]	1.262 (6.4)[b]	
t	1.726 (2.31)[b]	1.878 (2.31)[b] 1.912 (2.31)[b]	1.742 (2.31)[b]		1.535 (2.31)[b]	0.267 (2.31)[b] 2.108(2.31)[b]	1.235(2.31)[b]	

[a] The average of five experiments.
[b] The figures between parenthesis are the theoretical values of F and t at $P = 0.05$.
[c] [15] Spectrophotometric procedure, by dissolving in methanol and measuring the absorbance at 284 nm $E^{1\%}_{1\ cm} = 3.99 \times 10^2$.
[d] [16] HPLC method using Hypersil ODS column, acetonitrile, 0.1 M K_2HPO_4 adjusted to pH 7 with H_3PO_4 as mobile phase, detection at 290 nm.

when the molar ratio of Cu (II) to eosin was approximately 1:1 taking into consideration the determination of drug limits. This showed the importance of the concentrations of Cu (II) and eosin. The composition of the ternary complexes obtained by the molar absorptivity (ε), and the relative standard deviation (R.S.D., $n = 5$) are shown in (Table 2).

The effects of temperature and time were also studied. The color development at room temperature was very slow, more than 24 h have been required. Maximum absorbance was obtained at 60°C after 20 min for (I) and at 70°C after 25 min for (II). The solution was cooled for 5 min under tap water to about 25°C with agitation before measuring the absorbance. This was solubilizing jelly-like aggregates formed upon heating under the above described conditions. The absorbance of both (I) and (II) were measured at 549 nm. Calibration curves construction gave linear relationship for (I) and (II) in the concentration ranges 3.69–16.61 μg ml^{-1} for (I) and 4.3–25.9 μg ml^{-1} for (II) with mean percentage recoveries of 99.76 and 99.46% and relative standard deviation of 0.36 and 0.81 for (I) and (II), respectively as shown in (Table 2). The sensitivity ranges, molar absorptivity, regression equations, correlation coefficient and mean accuracy percentages for the method are shown in (Table 2). The molar ratio for both (I) and (II) Cu:eosin:drug was 3:3:1.

When the proposed methods were applied to the analysis of the commercial capsules and tablets, the validity was assessed applying the standard addition technique and the results obtained are shown in (Table 4). There was no evidence of interference from the excipients.

The results of the proposed methods were statistically compared with those obtained by the reported methods [15,16]. The data in (Table 5) shows that the calculated F and t values were less than the theoretical ones, confirming accuracy and precision at the 95% confidence level.

4. Conclusion

The suggested methods have the advantages of being simple, accurate, sensitive and suitable for routine analysis in control laboratories. DDQ and iodine methods utilize a single step reaction and single solvent. The iodine acceptor method was more sensitive in the case of lansoprazole than pantoprazole as mentioned above. The ternary complex method did not require prior extraction procedure and have the advantages of sensitivity, simplicity and reproducibility. All these methods can be used as general methods for the spectrophotometric determination of lansoprazole and pantoprazole sodium sesquihydrate in bulk and in pharmaceutical formulations. They are convenient for quality control and routine determination of these drugs.

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