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DEVELOPMENT AND VALIDATION OF SPECTROPHOTOMETRIC METHODS FOR DETERMINATION OF CERTAIN PROTON PUMP INHIBITORS

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ABSTRACT

Two simple, sensitive and economic spectrophotometric methods, A and B, were developed for the determination of certain proton pump inhibitors. Method A is based on the reaction of esomeprazole (EMZ), lansoprazole (LNZ), and pantoprazole (PNZ) with molybdenum(v)-thiocyanate ion to form stable orange red colored ion pair complexes extractable selectively with methylene chloride. The orange red colored complexes showed maximum absorption at 468-470 nm. Method B is based on formation of colored products between the three studied drugs EMZ, LNZ, PNZ and 4-chloro-7-nitrobenzofurazan (NBD-Cl) in methanol medium at 70 ± 2 °C. The absorbence of the yellow colored product was measured at 382-390 nm. Optimization of the various experimental conditions is described. Under the optimized experimental conditions, Beer's law was obeyed in the concentration ranges 5-60, 7-60 and 6-60 for method (A) and 2 - 10 μg ml^{-1} (methods B) for the three drugs. Results obtained by applying the proposed methods showed good recoveries of 99.86 ± 1.02 %, 99.66 ± 1.23 % and 100.10 ± 1.10 % for method A and 100.24 ± 1.18 %, 100.03 ± 1.08 % and 99.63 ± 0.61 %, method B, for the three mentioned drugs. The developed methods were applied for determination of the studied drugs in their pharmaceutical preparations with good accuracy and precision. The obtained results were compared favorably with reference spectrophotometric method indicating no significant d fference between the methods compared. Thus, the proposed spectrophotometric methods can be applied as inexpensive, rapid, easy, accurate and precise methods for the routine analysis of the three proton pump inhibitors in pharmaceutical preparations.

INTRODUCTION

Esomeprazole magnesium trihydrate is chemically bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridiny')methyl]sulfinyl]-1-H-benzimidazole-1-yl) magnesium trihydrate[1]. Lansoprazole is a substituted benzimidazole, it is officially listed in the USP and chemically known as methyl-4-(2,2,2-trifluroethoxy)-2-pyridyl] methyl]sulfinyl] benzimidazole [1,2]. Pantoprazole sodium sesquihydrate is chemically known as sodium 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-p-methyl]sulfinyl]-1H-benzimidazole sesquihydrate [1], it is a non official drug and not listed at any pharmacopoeia (USP or BP or Ph Eu or IP). These drugs are belonging to class of antisecretory compounds. They are referred to as proton pump inhibitors (PPIs) and were introduced for the management of duodenal ulcer, gastric ulcer or pathogenic hypersecretory condition [1]. Gastric PPIs are absorbed in the small intestine and reach via systemic circulation, to gastric parietal cells, where they bind to proton pump (H^+/K^+ATPase) and disturb the function of proton pump, thereby resulting in a potent acid inhibition [3].

Esomeprazole is the S-isomer of omeprazole, the first single optical isomer PPI generally provides better acid control than current racemic PPIs and has a favorable pharmacokinetic profile relative to omeprazole [1]. The drug is officially listed in Martindale: The Extra Pharmacopoeia. It is not cited in any pharmacopoeia (USP or BP or Ph Eu or IP) and the available literature for its determination are GC-MS [4], HPLC [2] and spectrophotometeric methods [5,6].

Literature survey of lansoprazole has revealed several analytical methods for its determination in biological fluids and in pharmaceutical formulations. These include; high-performance liquid chromatography (HPLC) [7-11], electrochemical [12,13] and spectrophotometric methods [14-16].

The reported methods for determination of pantoprazole in pharmaceutical formulations and in biological fluids were, high performance liquid chromatography (HPLC) [17-19], TLC densitometry [20], capillary electrophoresis [21], derivative UV-spectrophotometry [22], difference UV-spectrophotometry [23] and visible spectrophotometry [24-28].

Owing to the vital importance of the studied drugs, development of sensitive, simple and fast methods for their determination is needed. Spectrophotometry is the technique of choice, even today, in the laboratories of research, hospitals and pharmaceutical industries due to its low cost and inherent simplicity. Survey of literature revealed that very limited methods are available for the spectrophotometric determination of EMZ, LNZ and PNZ in formulations. The present work aims to demonstrate two simple, accurate, sensitive and selective visible spectrophotometric methods, (A and B) suitable and convenient for the determination of the studied drugs in pure form and in pharmaceutical preparations. Method A is based on the reaction of EMZ, LNZ and PNZ with Molybdenum(V)-thiocyanate ion to form stable orange red colored ion pair complexes, which were selectively extracted with methylene chloride. On the other hand, method B is based on formation of colored reaction products between the three studied drugs EMZ, LNZ and PNZ with 4-chloro-7-nitrobenzofurazan (NBD-Cl) in methanol medium at 70 °C. The developed colored products were measured spectrophotometrically. The developed methods were validated according to the current ICH guidelines [29].

EXPERIMENTAL

Reagents and chemicals:

All reagents were of analytical reagent grade and used without further purification and water was doubly distilled.

- Molybdnum(VI) solution, 1 x 10^{-3} M was prepared by dissolving appropriate weight of ammonium Molybdate tetrahydrate in water

- Ammonium thiocyanate (10% w/v) aqueous solution was used
- Ascorbic acid (10% w/v) aqueous solution was also prepared
- Hydrochloric acid 3.0 M solution was used
- NBD-Cl (Aldrich product) solution in methanol (2.0 mg ml^{-1}) was prepared.

Pure Sample:

- Esomeprazole magnesium was obtained from AstraZeneca group of companies, AstraZeneca, Cairo, Egypt
- Lanzoprazole was from Sedico Pharmaceutical Co., Egypt.
- Pantoprazole sodium sesquihydrate was obtained from Medical Union Pharmaceuticals, Abu-Sultan, Ismailia, Egypt.
- Stock solution of drugs 1.0 mg ml^{-1} were prepared in 0.1 M hydrochloric acid, for method A and in methanol for method B. Standard working solution of drugs was prepared every day by diluting the stock solution with 0.1 M hydrochloric acid and methanol.

Pharmaceutical preparations:

- Nexium® 40 mg tablets, labeled to contain 40 mg of esomeprazole per each tablet, were obtained from AstaZeneca group of companies, AstraZeneca, Cairo, Egypt
- Zollipak® capsules (Sedico Pharmaceutical Co., Egypt), each capsule labeled to contain 30 mg of lansoprazole
- Lanzor® 30 mg capsules were from Aventis Pharma. S.A.E under licence of Aventis Pharma - Germany
- Pantoloc® 40 mg tablets were obtained from Medical Union Pharmaceuticals, Abu-Sultan, Ismailia, Egypt. Each tablet was labeled to contain 40 mg pantoprazole

Apparatus

UV/Vis spectrophotometer Uvidec-610 type with 1.0-cm matched cell (Shimadzu, Tokyo, Japan) was employed for measuring the absorbance values.

General procedure:

Method A:

Into 50 ml separating funnel, 1.5 ml ammonium molybdate reagent, 5.0 ml of 3.0 M HCl, 1.5 ml ascorbic acid and 2.0 ml ammonium thiocyanate solution were mixed and left for 10 min at room temperature. Appropriate volumes of working solutions in the concentration ranges stated, in table 1, were added and left for another 10 min. Extract with 10 ml methylene chloride (twice, 5.0 ml portions), the mixture was shacken well for 1.0 min and allowed to separate into two phases. Methylene chloride extracts were dried over anhydrous sodium sulphate and absorbance values were measured at 468- 470 nm against reagent blank prepared similarly without the drugs.

Method B:

Aliquots containing 50.0 – 600.0 µg of the working solution in methanol were transferred into 10.0 ml calibrated flasks. 1.0 ml of 2.0 mg/ml solution of NBD-Cl was added and heated on water bath at 70 ± 2 °C for 10 min. After cooling, the mixture was diluted to the mark with methanol. The absorbance of the colored products were measured at 382- 390 nm against reagent blank prepared in the same manner.

Procedure for pharmaceutical preparations:

Twenty tablets were weighed and powdered. An accurately weighed portion of powdered tablets equivalent to 20 mg (method A) or 100 mg (method B) of drugs were dissolved in 60 ml 0.1 M HCl or methanol, completed to 100-ml volume with the same solvent, filtered, and the first few milliliters of the filtrate were discarded. Accurately measured volumes of the filtrate were assayed as described under the general procedure A and B.

Twenty capsules each of Nexium or Pantoloc were emptied carefully and the mass of the collected contents were finely powdered in a mortar. An accurately weighed quantity equivalent to 20 mg (method A) or 100 mg (method B) of the powdered drug mixtures were dissolved in about 60.0 ml 0.1 M HCl (method A) or methyl alcohol (method B), completed to 100-ml volume with the same solvent and filtered. Aliquot volumes of the filtrate, in the concentration ranges stated in table 1, were treated as stated under the general procedure A or B described earlier.

RESULTS AND DISCUSSION

Method A:

Formation of ternary complexes between the tertiary amine group and Mo(V)-thiocyanate binary complex occurs via the protonated nitrogen atom. Mo(V) formed by reduction of Mo(VI) with ascorbic acid, combined with ammonium thiocyanate in 0.8 – 3.2 M HCl solutions [30, 31].

In this study ternary complexes were formed between tertiary amino groups of drugs EMZ, LNZ, PNZ and Mo(V) – thiocyanate binary complex via protonated nitrogen atoms of the cited drugs. Reaction of Mo(VI) with ammonium thiocynate in 3.0 M HCl, in the presence of ascorbic acid and subsequent reaction with the studied drugs is suggested to be as shown in scheme 1. The formed ternary complexes were soluble in methylene chloride while Mo(V) – thiocyanate binary complex was insoluble. Double extractions were sufficient to extract the ternary complexes quantitatively into the organic phase. These ternary complexes showed absorption maximum at 468- 470 nm in methylene chloride (Fig. 1).

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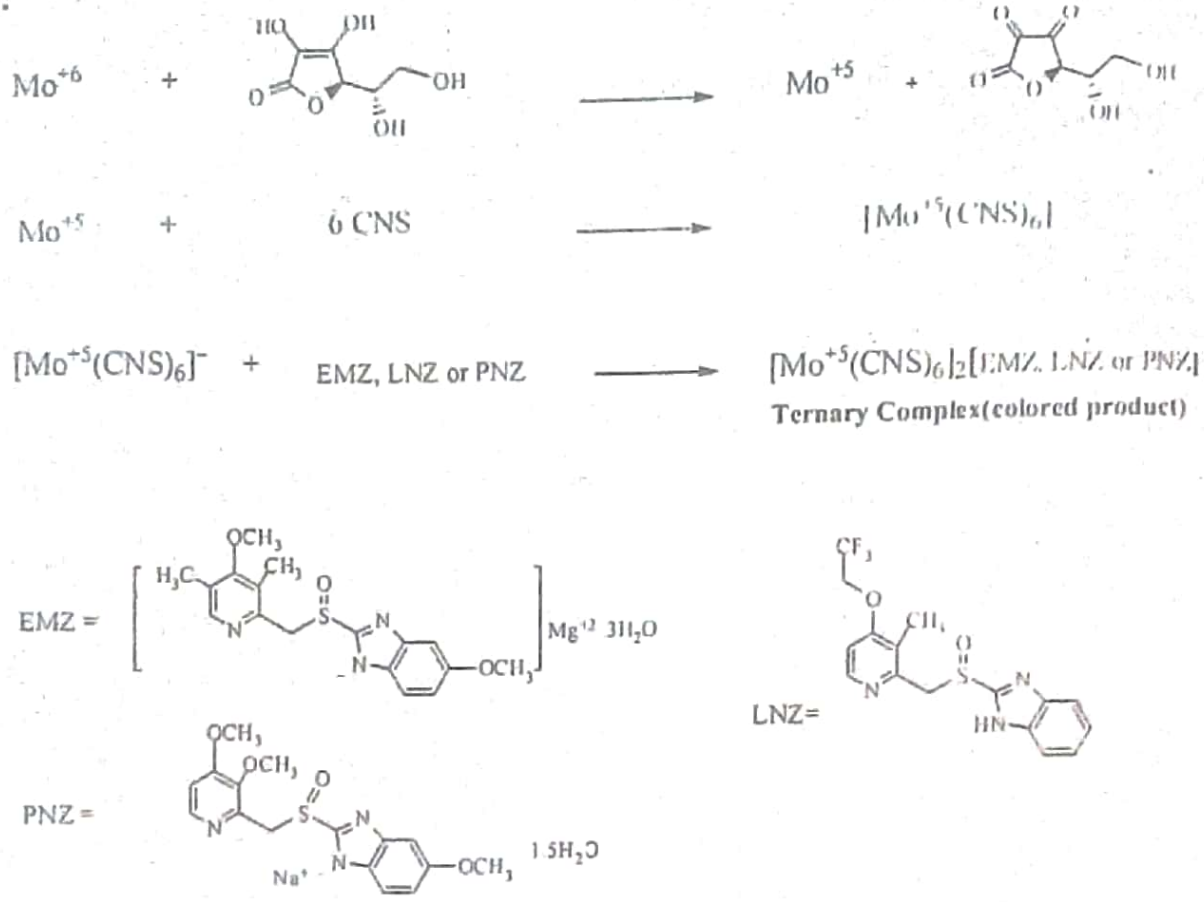
Scheme 1:



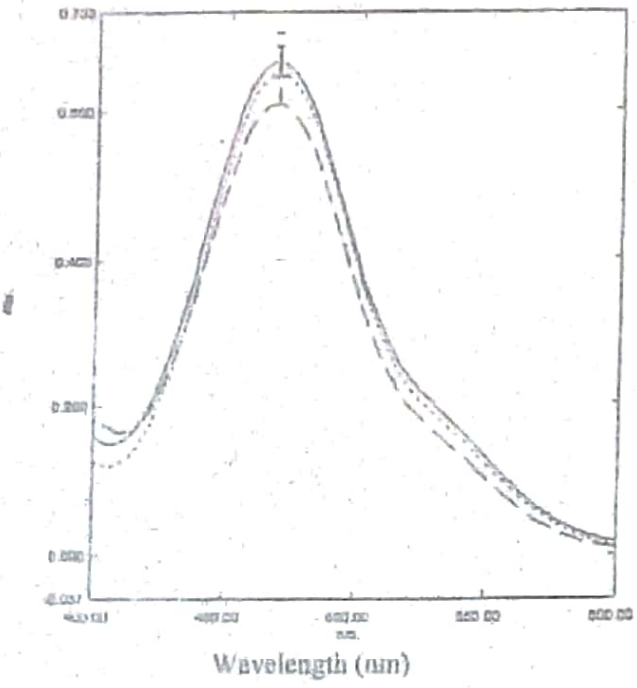


Fig. 1: Absorption spectra of the colored reaction products of EMZ; (doted line), LNZ (dashed line) and PNZ (solid line), for EMZ, LNZ and PNZ (40 µg ml^{-1}) complexes with $[Mo(CNS)_6]^-$

Optimization of the reaction variables:

Method A;

Hydrochloric acid has been selected as the suitable medium for the ternary complexes formation and extraction [32]. 5.0 ml of 3.0 M HCl was found sufficient for the formation of Mo(V) thiocyanate - EMZ, LNZ and PNZ complexes.

The effect of ammonium Molybdate tetrahydrate and the ternary complex formation was studied. It was found that 1.5 ml of 1×10^{-3} M reagent was sufficient for maximum absorbance for the stated concentration ranges for drugs EMZ, LNZ and PNZ. After that, the absorbance was nearly constant. 1.5 ml ascorbic acid (10% w/v) and 2.0 ml ammonium thiocyanate (10% w/v) were found to be sufficient to produce maximum absorbance for the studied drugs. In this method complete formation of the ternary complexes needs 10.0 min before extraction with methylene chloride at room temperature.

Methylene chloride, chloroform, and dichloroethane extract the ternary complex quantitatively. Methylene chloride was found to be more suitable with respect to stability and high solubility of the ternary complex in it. Moreover, double extraction with 10.0 ml (5.0 ml portion) and 1.0 min shaking time gave quantitative results.

Calibration graphs were constructed under the optimized reaction conditions for the studied drugs. Beer's law was obeyed over the concentration ranges of 5-60, 7-60 and 6-60 µg ml^{-1} for EMZ, LNZ and PNZ, respectively. The molar absorptivity for the formed

ternary complexes in methylene chloride were 0.61×10^{4}, 0.50×10^{4} and 0.62×10^{4} L mol^{-1} cm^{-1} for EMZ, LNZ and PNZ, respectively at λ_{max} 468-470 nm. Moreover, Sandell sensitivity, slope , intercept and correlation coefficient for each drug were calculated and tabulated in table 1.

Table (1): Characteristic parameters for the proposed spectrophotometric methods A and B.

Parameter	Method A			Method, B		
	EMZ	LNZ	PNZ	EMZ	LNZ	PNZ
λ_{max} (nm)	468-470	468-470	468-470	384-386	382-384	382-384
Stability of colored products (hrs)	12	12	12	8.0	8.0	8.0
Beer's law limits (µg ml^{-1})	5 - 60	7 - 60	6 - 60	1.5 - 10	1.5 - 10	2 - 10
LOD (µg ml^{-1})	1.37	1.49	1.48	0.57	0.6	0.62
LOQ (µg ml^{-1})	4.16	4.53	4.49	1.5	1.8	1.87
Sandell sensitivity (µg cm^{-2})	5.66×10^{-2}	7.4×10^{-2}	6.23×10^{-2}	9.44×10^{-3}	1.09×10^{-2}	1.16×10^{-2}
Molar abs. ε (L mol^{-1} cm^{-1})	0.61×10^{4}	0.51×10^{4}	0.62×10^{4}	3.7×10^{4}	3.4×10^{4}	3.3×10^{4}
Regression equation[a]						
Slope (a)	-0.01276	0.01483	0.02263	-0.0646	-0.0400	-0.0325
Intercept (b)	0.01795	0.01339	0.01575	0.1120	0.0980	0.1840
Correlation coefficient (r)	0.9998	0.9999	0.9996	0.9996	0.9998	0.9997
Recovery (%)	99.86	99.66	100.1	100.24	100.03	99.63
Standard deviation (S.D)	1.02	1.23	1.10	1.186	1.080	0.610
Relative S.D. (R.S.D%)	1.021	1.234	1.099	1.183	1.080	0.612
Student t-test[b] (2.57)[c]	0.65	0.18	1.12	1.21	0.56	0.49
Variance F-value[b] (5.05)[c]	1.88	2.03	1.08	2.54	2.63	2.02

[a] $A = a + bC$, Where C is the concentration in µg ml^{-1}.
[b] Compared with the reported spectrophotometric method [6].
[c] Values in parenthesis are the theoretical t- and F-values for five degrees of freedom and 95% confidence limits.

Method B:

In this method Esomeprazole magnesium, Lanzoprazole and Pantoprazole were determined colorimetrically by the formation of methanolic soluble colored reaction products, suggested to be charge transfer complexes, with NBD-Cl. The absorbance values of the complexes were measured at their maximum wavelengths 385-390 nm. As shown in Fig. 2. Investigations were carried out to establish the most favourable conditions for the charge transfer formation. The effect of some variables on the reaction has been tested as follows.

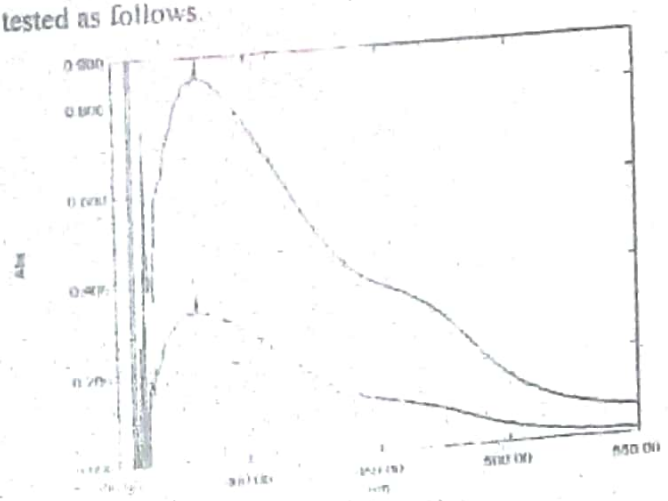


Fig. 2: Absorption spectra of the colored reaction products of EMZ (8 µg ml^{-1}) and PNZ (3.5 µg ml^{-1}) with NBD-Cl in methanol

Effect of reagent concentration

The amount of NBD-Cl necessary to obtain linear graph for drug concentrations were studied. When various concentrations of the reagent were added to the studied drugs, 1.0 ml of 2.0 mg/ml NBD-Cl solution was found to be sufficient for the production of maximum and reproducible color intensity.

Effect of time and temperature

No reaction has been found at room temperature. Whereas complete color development was attained after 10 min on raising the temperature to 70 °C on water bath to obtain complete color development. The color remained stable for more than 12 hrs for all the studied drugs.

Effect of solvents

Several organic solvents e.g. methanol, ethanol, propanol, acetone, dioxane, acetonitrile and dimethylformamide (DMF) were investigated. Methanol was found as the best solvent for the formation of charge transfer complexes between the studied drugs and NBD-Cl

Quantification

Linear correlations were obtained between absorbance and concentration in the range given in table 1. Molar absorptivities, Sandell sensitivities, slopes, intercepts and correlation coefficients are also given in table 1.

The most important spectral characteristics of the reaction of EMZ, LNZ and PNZ with NBD-Cl are presented in table 1. Relative standard deviations and ranges obtained are also given in table 1.

Limits of detection LOD (K= 3) and of quantification LOQ (K= 10) of the methods were established according to the IUPAC (LOD = KS/s) S is the standard deviation of blank determination, s is

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the slope of the standard curve and K is a constant related to the confidence interval [32]. Values are calculated and recorded in table 1.

Performance of the proposed methods were assessed by calculation of t- and F- values compared with reported spectrophotometric method [6]. Results are tabulated in table 1 showed that calculated t- and F-values did not exceed theoretical values. Comparison of recoveries obtained with the proposed methods with the purity of the studied drugs as determined according to the reported methods showed high accuracy of the proposed methods. They are simpler, less time consuming and more sensitive than the reported method. Moreover the proposed methods could be used for routine determination of EMZ, LNZ and PNZ in pure form or in their pharmaceutical formulations. The relative standard deviation of the proposed methods were 1.021, 1.234, 1.099 for method A and 1.183, 1.080, 0.612 for method B, respectively (six determinations). Percentage recoveries of the proposed procedures were 99.86, 99.66, 100.10 for method A and 100.24, 100.03, 99.63 for method B, respectively table 1. Results were compared statistically using F- and t- tests. The calculated F- and t- values did not exceed the theoretical values. Therefore, it is concluded that there is no significant difference between the proposed methods and the reported reference method with respect to repeatability (F-test) and accuracy (t-test).

Application to pharmaceutical preparations:

The applicability of the method to assay pharmaceutical preparations was examined. Commercial capsules /or tablets containing EMZ, LNZ and PNZ were successfully analyzed by the proposed methods. Results, in table 2 & 3, indicate high accuracy of the proposed methods for determination of the studied drugs. They have the advantages of being free from interferences by common excipients. Results showed good agreement with those of the reported method [6]. Table 3 shows the results of assay and reveals that there is close agreement between the obtained results by the proposed methods and the label claim. Results were also compared statistically with those obtained by reference method [6] by applying student's t-test for accuracy and F-test for precision. At the 95 % confidence level, the calculated t- and F-values did not exceeds the theoretical tabulated values, indicating no significant difference between the methods compared.

Table 2: Results of determination of EMZ, LNZ and PNZ in different pharmaceutical preparations using the standard addition techniques for methods A and B.

Dosage form	Method A			Method B			Reference method [6]
	Taken µg ml^{-1}	Added µg ml^{-1}	Recovery%*	Taken µg ml^{-1}	Added µg ml^{-1}	Recovery%*	Recovery%*
Nexium® tablets (40 mg EMZ)	10	--	99.7	2	--	99.6	99.4
		5	101.2		2	98.9	97.9
		10	99.7		3	99.3	99.2
		20	100.1		4	99.5	98.9
		30	99.8		5	99.8	99.6
		40	100.8		6	100.0	
		50	99.47		7	99.2	
Zollipak® capsules (30 mg LNZ)	10	--	99.8	2	--	99.8	98.2
		5	99.2		2	98.9	99.1
		10	98.8		3	99.6	97.6
		20	100.7		4	99.0	97.8
		30	101.1		5	99.1	99.6
		40	100.2		6	100.6	
		50	99.7		7	101.1	
Lanzor® capsules (30 mg LNZ)	10	--	99.7	2	--	99.8	98.3
		5	99.5		2	98.8	98.6
		10	99.8		3	99.4	99.2
		20	99.7		4	100.2	100.0
		30	100.0		5	100.6	99.0
		40	99.8		6	101.0	
		50	100.4		7	99.9	
Pantoloc® tablets (40 mg PNZ)	10	--	99.7	3	--	99.7	100.1
		5	98.4		2	99.5	99.5
		10	98.9		3	99.8	99.7
		20	99.6		4	100.3	97.8
		30	99.7		5	100.6	98.7
		40	100.1		6	98.7	
		50	99.3		7	99.6	

*Average of three determinations.

Table 3: Comparison of the results obtained by the proposed methods with that obtained by the reported method [6] for determination of EMZ, LNZ and PNZ in their different pharmaceutical preparations.

Dosage form	Obtained results		
	Method A	Method B	Reported method [6]
Nexium tablets (EMZ)			
Mean recovery	100.17	99.45	99.00
S.D	1.49	0.82	1.20
R.S.D%	1.49	0.83	1.21
S.E.	0.67	0.33	0.54
Variance	2.23	0.67	1.44
F-value	1.55	2.15	
t-test	0.73	0.74	
Zollipak capsules (LNZ)			
Mean recovery	99.95	99.87	98.44
S.D.	1.25	1.789	1.72
R.S.D%	1.25	1.791	1.75
S.E.	0.56	0.80	0.77
Variance	1.57	3.20	2.96
F-value	1.89	1.08	
t-test	1.68	1.37	
Lanzor capsules (LNZ)			
Mean recovery	99.87	99.98	99.02
S.D	0.60	1.66	1.16
R.S.D%	0.60	1.66	1.17
S.E	0.25	0.68	0.52
Variance	0.36	3.76	1.35
F-value	3.25	2.79	
t-test	1.58	0.97	
Pantodac tablets (40 mg PNZ)			
Mean recovery	99.33	99.75	99.16
S.D	1.25	1.30	1.82
R.S.D%	1.26	1.30	1.84
S.E	0.51	0.53	0.81
Variance	1.56	1.69	3.31
F-value	2.12	1.96	
t-test	0.38	0.63	

[a] Average of three determinations.

Method validation;

Accuracy and precision;

Intra-day and inter-day precisions were assessed from the results of six replicate analyses on pure drug solution. The mean values and relative standard deviation (RSD) values for replicate analyses at three different concentration levels were calculated. To calculate the inter-day precision, analysis was performed over a period of five days preparing all solutions, fresh each day. The accuracy of the methods was determined by calculating the percentage deviation observed in the analysis of pure drug solutions and expressed as the relative standard deviation (RSD). Table 1 and 4 summarize the intra-day and inter-day precision and accuracy data for the determination of the studied drugs by the proposed methods.

Accuracy and validity of the methods were further ascertained by performing recovery experiments via standard addition technique. To a fixed and known amount of PNT in tablet powder (pre analysed), pure drug was added at three levels and the total was found by the proposed methods. Each test was repeated three times. The recovery of pure drugs added to tablet powder ranged from 99.33 to 100.17 % (Table 4) indicating that commonly encountered tablet excipients and additives did not interfere in the assay procedures.

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Table 4. Evaluation of accuracy and precision to the studied drugs applying standard addition technique by the proposed methods.

Method	EMZ		LNZ		PNZ	
	Taken, μg ml^{-1}	Found* μg ml^{-1}	Taken, μg ml^{-1}	Found* μg ml^{-1}	Taken, μg ml^{-1}	Found* μg ml^{-1}
Method A	15.0	14.90	15.0	14.92	15.0	14.90
	30.0	29.95	30.0	29.90	30.0	30.02
	45.0	44.85	45.0	44.55	45.0	44.65
Mean recovery%		99.60		99.38		99.54
S.D.		0.382		0.538		0.750
R.S.D.%		0.384		0.541		0.753
Method B	3.0	2.97	3.0	2.96	3.0	2.99
	5.0	4.98	6.0	6.01	6.0	5.96
	7.0	7.01	8.0	7.97	8.0	8.02
Mean recovery% S.D.		99.58		99.49		99.76
R.S.D.		0.820		1.080		0.742
		0.824		1.087		0.744

*Mean value of six determinations.

CONCLUSION

The proposed methods were more preferable over the other reported method with respect to sensitivity, simplicity, accuracy, precision and stability of the colored species up to 12 hrs. The proposed methods can be applied for the routine analysis and in quality control laboratories for the quantitative determination of the studied drugs in pure form and in pharmaceutical preparations depending upon availability of the chemicals and instruments. Various additives and excipients that often accompany antiulcer drugs in pharmaceutical preparations such as lactose, glucose, starch, gum acacia, magnesium stearate and talc did not interfere.

Although HPLC methods have higher selectivity, they require complicated sample pre-treatment and use expensive apparatus. The developed methods have advantages of economy, wider range of determination, less time consumption with high accuracy and precision. The proposed methods have advantages of; sensitivity, selectivity, ease of performance, economy, wider range of determinations, less time consumption, high accuracy and precision compared to the official [2] and reported reference methods [6].

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تطوير و اعتماد طرق لونية لتحليل بعض مضادات الحموضة فى صورتها النقية و فى مستحضراتها الصيدلية

جمال حسن رجب

قسم الكيمياء التحليلية – كلية الصيدلة – جامعة الزقازيق – الزقازيق – مصر

يصف هذا البحث طريقتين لونيتين تمتاز بالسهولة والحساسية والدقة لتقدير إسوميبرازول و لانزوبرازول و بانتوبرازول. تعتمد الطريقة الأولى على تكوين معقد ثلاثى بين الأدوية المذكورة و الموليبدنم الخماسى و الثيوسيانات فى وسط حامضى.وقد تم استخلاص المعقد الثلاثى بواسطه كلوريد المثيلين وتم قياس اللون الاحمر البرتقالى الناتج عند طول موجه قدره 468-470 نانو متر. وكان معامل الامتصاص الجزيئى مساويا 0.6و0.5 و0.62 *410 لتر / مول/ سم لكل من الأدوية المذكورة على التوالى. . والطريقه المستخدمه تتبع قانون بير عند تركيزات من 5 – 60و7 الى 60و 6 الى 60 ميكروجرام لكل 1 ملليلتر بالنسبه لإسوميبرازول و لانزوبرازول و بانتوبرازول على التوالى . وتعتمد الطريقه الثانية على استخدام 4 – كلورو- 7 - نيترو - 2 , 1 , 3بنزوكسادبازول في وسط لا مائي عن طريق تكوين مركب ناقل للشحنات بين هذه المركبات كمعطية للالكترونات وبين المستقبل 4 - كلورو -7 - نيترو - 2 , 1 , 3بنزوكسادبازول كساحب للالكترونات مكونا لون برتقالي تم قياسه عند طول موجي 384-390 للأدوية المذكورة. وقد تمت دراسة الظروف المختلفة التى تعطى نتائج مرضية ووجد أن التفاعل يتبع قانون بير في مدى تركيز يتراوح من 2 - 10 ميكروجرام / مل للأدوية المذكورة وقد تم عمل تحليل احصائى للطرق المقترحة بالمقارنة بالطرق الدستورية والمرجعية للادوية المقترحة ووجد أن الطرق المقترحة لا تختلف تقريبا عن الطرق التي تقارن بها . وقد تم تطبيق الطرق المقترحة بنجاح لتحليل العقاقير المذكورة في المستحضرات الصيدلية المحتوية عليها.