Journal of Food and Drug Analysis

Volume 12 | Issue 2 Article 12

2004

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Journal of Food and Drug Analysis, Vol. 12, No. 2, 2004, Pages 102-109 藥物食品分析 第十二卷 第二期

Anodic Polarographic Determination of Lansoprazole and Omeprazole in Pure form and in Pharmaceutical Dosage Forms

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(Received: October 8, 2003; Accepted: November 14, 2003)

ABSTRACT

Lansoprazole (LNS) and omeprazole (OMP) are therapeutically important drugs, and the need arose for a simple, reliable method for their content uniformity of their tablets. The anodic polarographic behavior of lansoprazole and omeprazole has been studied in Britton-Robinson buffer (BRb) over the pH range 4.1-11.5. In BRb of pH 7 well-defined anodic waves were produced with diffusion-current constant (Id) of 1.70 ± 0.01 (n = 6) and 1.66 ± 0.01 (n = 8) for LNS and OMP, respectively. The current-concentration plots were rectilinear over the ranges of 4-24, 2-16 μg mL^{-1} using Direct Current (DC_t) mode for LNS and OMP, respectively and over the range 2-18, 0.4-12 μg mL^{-1} using the Differential Pulse Polarographic (DPP) mode for LNS and OMP, respectively. The detection limits (S/N = 2) using DPP mode were 0.2 μg mL^{-1} (5.41×10^{-7} M) and of 0.05 μg mL^{-1} (1.45×10^{-7} M) for LNS and OMP, respectively. The proposed method was successfully applied to the analysis of the two drugs in their commercial capsules. The average percent recoveries were favorably compared to those obtained by reference methods, with satisfactory standard deviations. A pathway for the electrode reaction in both cases was postulated. The proposed method is characterized by being simple, accurate and stability-indicating.

Key words: lansoprazole, omeprazole, dosage forms, polarography, anodic current mode

INTRODUCTION

Lansoprazole 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulphinyl]-1 H-benzimidazole, is a new proton-pump inhibitor with action and uses similar to those of omeprazole. Lansoprazole has been demonstrated to be effective in the treatment of duodenal and gastric ulcers, where inhibition of gastric acid secretion may be beneficial [(1)].

Relatively few methods have been described for the quantitative determination of lansoprazole in formulations and biological fluids, viz., spectrophotometry[(2,3)], capillary electrophoresis[(4)] and HPLC[(5-12)]. A cathodic polarographic method has been described for the determination of lansoprazole in capsules and spiked urine[(13)]. The method is not stability-indicating as it is subject to interference by degradation products. In the anodic mode of polarography, the analytes are less subject to interference likely to be introduced by common excipients, decomposition products and related compounds.

As for omeprazole, 5-Methoxy-2-{[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl}-1H-benzimidazole, it is a benzimidazole derivative which inhibits gastric acid secretion. It acts by interaction with H^+ K^+ ATpase in the secretory membranes of the parietal cells and is very effective in the treatment of Zollinger Ellison Syndrome. Although its elimination half-life from plasma is short (reported to be about 0.5 to 3 hr), its duration of action with regard to inhibition of acid secretion is much longer allowing it to be used in single daily dose[(1)]. Several methods have been utilized for the quantitative estimation of OMP in pharmaceutical preparations and biological fluids, including: spectrophotometry[(14-17)], capillary electrophoresis[(18,19)], voltammetry[(20-23)], HPLC[(24-28)] and TLC[(29)].

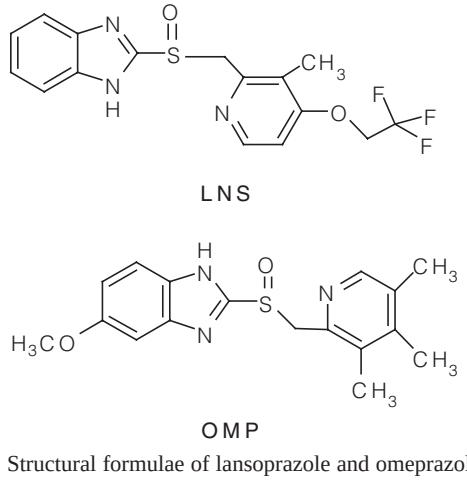

Figure 1. Structural formulae of lansoprazole and omeprazole.

Recently the electrochemical oxidations of lansoprazole and omeprazole have been studied at a carbon paste electrode by cyclic and differential pulse voltammetry[(30)]. The linear range is 2×10^{-7} to 5×10^{-5} M with detection limits of 1×10^{-8} and 2.5×10^{-8} M for LNS and OMP, respectively.

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In this piece of work, the anodic oxidation of the studied compounds at the Dropping Mercury Electrode (DME) has been exploited for developing a simple and reliable method for their determination in dosage forms. The method is satisfactorily accurate and precise and is comparable to reference methods. Its major advantage is its stability-indicating nature. The degradation of lansoprazole and omeprazole is reported to produce the corresponding sulphide[31]. The latter is not readily oxidized at the DME, therefore, the proposed method can be considered as a stability-indicating assay for the two drugs.

MATERIALS AND METHODS

I. *Apparatus*

The polarographic study and Differential Pulse Polarograhic (DPP) measurements were carried out using the Polarecord E 506 Metrohm (Herisau, Switzerland). The drop time of 1 sec was electronically controlled using a 663 VA Stand from the same company. The polarograms were recorded using a potential scan rate of 10 mV/sec. A three-electrode system composed of a dropping mercury electrode (DME) as the working electrode, $Ag^{\circ}/AgCl$ as reference electrode, and a graphite rod as the auxiliary electrode, was used. Polarograms were scanned between -0.4 to +0.4 V vs $Ag^{\circ}/AgCl$ electrode. The solutions were purged with pure nitrogen gas for 5 min before being polarographed at room temperature.

II. *Materials and Reagents*

(I) Lansoprazole and omeprazole were kindly provided by Aventis Pharma, Cairo, Egypt and were used as received. Lopral capsules each containing 30 mg of lansoprazole (Batch. No. 010378) and Gasec capsules each containing 20 mg of omeprazole (Batch. No. 010097) were obtained from commercial sources in the local market.
(II) Britton Robinson buffers (BRb) 0.08 M, covering the pH range 4.1-11.5[32].
(III) Methanol: AR grade (Aldrich, USA).
(IV) Diethyl ether: AR grade (Aldrich, USA).
(V) Dichloromethane (BDH, Poole, England).

(I) *Standard solutions*

Stock solutions containing 200 µg mL^{-1} of LNS and OMP were prepared in methanol and were further diluted with the same solvent to give the appropriate concentrations. The solutions were stable for five days when kept in the refrigerator. The methanol concentration in the polarographic cell was kept always at 20% of the total volume used.

III. *Calibration Graph*

Transfer aliquot volumes of the studied compounds covering the working range (cited in table 2) into 25-mL volumetric flasks. Complete to the mark with BRb of pH 7.0. Pass pure nitrogen gas for 5 min. Record the anodic DCt and DPP polarograms over the range -0.4 to +0.4 V vs Ag°/Ag Cl reference electrode, using a pulse amplitude of 70 mV in case of DPP mode. Plot the final concentration of the drugs (µg mL^{-1}) versus the current (µA) to get the calibration graph. Alternatively, derive the corresponding regression equations.

IV. *Procedure for Capsules*

The contents of 10 capsules were mixed well and pulverized. A weighed quantity of the powder equivalent to 20 mg of the studied compounds was transferred into a small flask and extracted with 3×30 mL of methanol. The extract was filtered into a 100-mL volumetric flask. The conical flask was washed with few mLs of methanol. The washings were passed into the same conical flask and completed to the mark with the same solvent. Aliquot volumes covering the working concentration range were transferred into 25-mL volumetric flasks. The volume was completed with BRb of pH 7.0. The whole contents of the flask were poured into the polarographic cell. Pure nitrogen gas was passed for 5 min. The DC_t and DPP polarograms were recorded. The nominal content of the capsules was calculated using either the calibration graph or the corresponding regression equation.

RESULTS AND DISCUSSION

Figure 1 shows the typical polarograms of lansoprazole using both anodic (DC_t and DPP) mode in BRb of pH

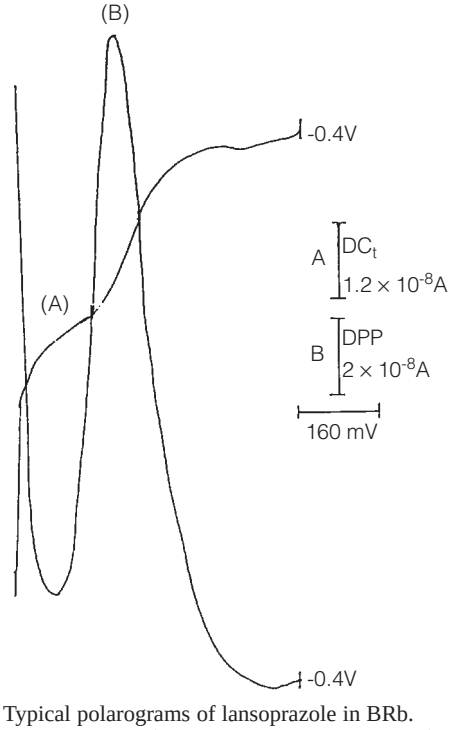

Figure 1. Typical polarograms of lansoprazole in BRb. (A) DC_t mode (24 µg mL^{-1}); (B) DPP mode (24 µg mL^{-1}).

7. Omeprazole behaves similarly. Methanol (in a ratio of 20% v/v) is added as solubilizer for the drugs, meanwhile, it decreases the adsorption phenomena likely to occur at the surface of DME. Both the DC_t and DPP peaks are sharp and steep and are therefore, suitable for quantitative determination of the drugs. Lansoprazole produces well-defined anodic waves over the pH range of 4.1-11.5 in BRb (Figure 2). Omeprazole behaves similarly.

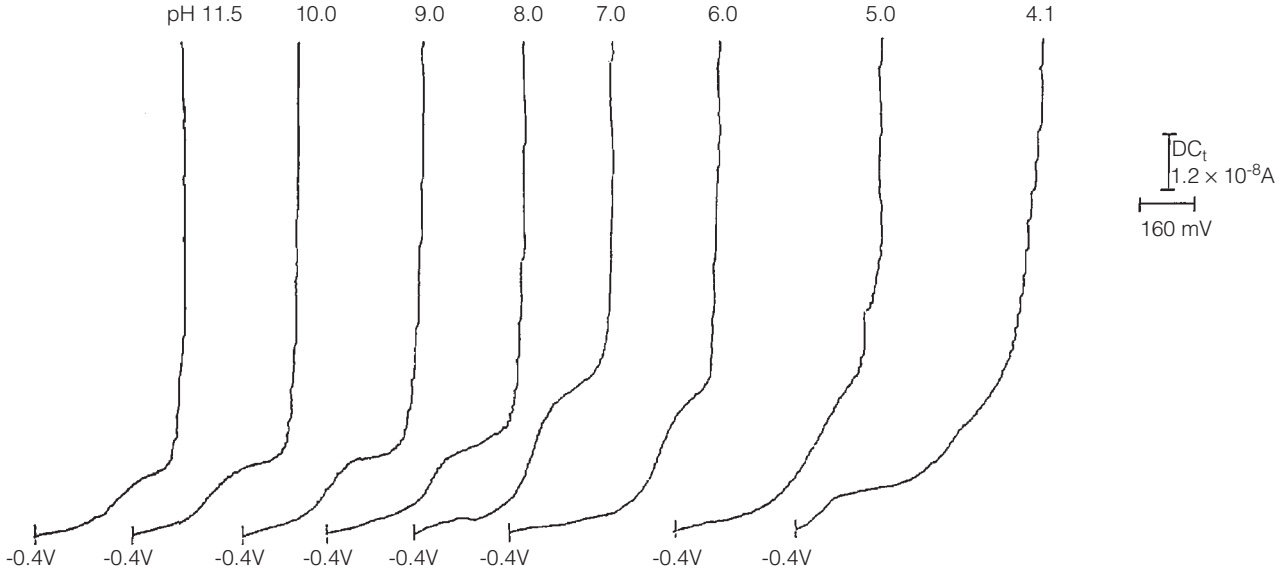

Figure 2. Effect of pH on the development of the polarographic waves of lansoprazole (20 μg mL^{-1}) using the anodic DC_t mode .

Table 1. Effect of pH on the development of the anodic polarographic waves of lansoprazole and omeprazole

Compound	pH	$E_{1/2}$	$\Delta E_{1/2}/\Delta$ pH	$W_{1/2}$ (mV)*	αn_a**,***
Lansoprazole	4.1	+ 86		200	0.45
			11		
	5.0	+ 76		230	0.47
			12		
	6.0	+ 64		160	0.59
			24		
	7.0	– 40		140	0.70
			– 32		
	8.0	– 72		150	0.53
			– 16		
	9.0	– 88		150	0.51
			– 8		
	10.0	– 96		160	0.46
			– 48		
	11.5	– 144		150	0.46
Omeprazole	4.1	+ 56		broad	0.70
			+ 44		
	5.0	– 16		160	0.622
			– 96		
	6.0	– 112		170	0.78
			– 42		
	7.0	– 154		140	0.93
			– 30		
	8.0	– 184		190	0.86
			– 16		
	9.0	– 200		140	0.70
			0		
	10.5	– 200		180	0.59
			0		
	11.2	–200		160	0.55

*$W_{1/2}$: the half peak width (mV) in the DPP mode.

**α: the transfer coefficient.

***n_a: the number of electrons transferred in the rate determining step.

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Logarithmic analysis of the oxidation waves of both compounds obtained in BRb of different pH values resulted in straight lines. The αn_a values were calculated according to the treatment of Meites and Israel[33], at pH 7.0 the αn_a values were found to be 0.70 and 0.93 for LNS and OMP respectively (Table 1). Assuming that the rate-determining step involves the transfer of two electrons, the values of the slopes point out to the completely irreversible nature of the electrode process.

I. *Study of the Wave Characteristics*

Increasing the mercury height (h) resulted in a corresponding increase in the waveheight (w) of both compounds in the anodic mode; plots of $\sqrt{h}$ *vs* the waveheight gave straight lines. Plots of log h *vs* log w gave straight lines, the slope of then were ~0.6. Changing the buffer concentration over the range 0.006 - 0.06 M resulted in a negligible decrease in the waveheight. These two characteristics point out to the diffusion-controlled nature of the waves of both compounds.

The alternating current-behavior (AC_t) of LNS was studied as a model example using a phase-selective angle of 90˚ (Figure 3). In BRb of pH 7, the summit potential (E_s) was shifted to more negative value of 180 mV than the corresponding $E_{1/2}$ value. Figure 3 shows that at this pH value, adsorption of the depolarizer only takes place while the reduction product is not adsorbed. OMP was found to behave similarly.

The studied compounds were found to be stable in BRb of pH 7 (the analytical pH) for about one and half hour at room temperature after which their waveheights began to decrease slowly.

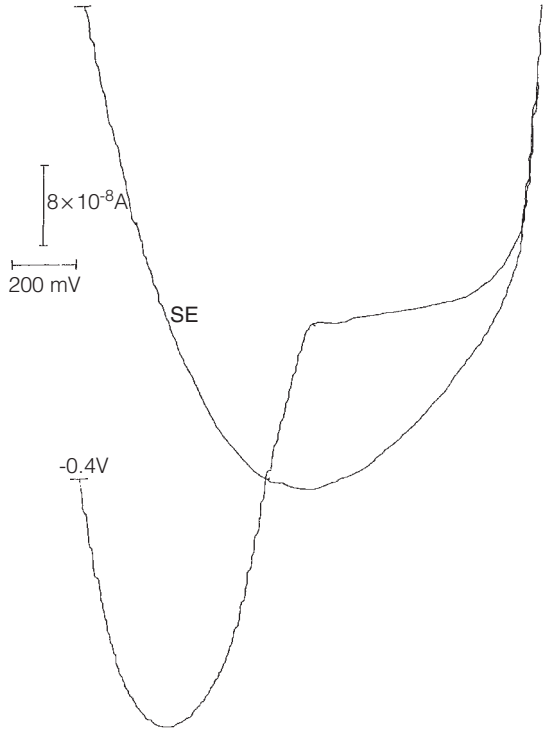
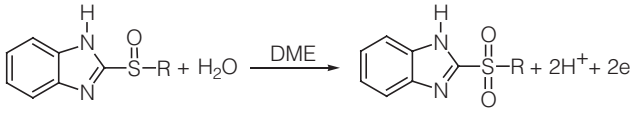


Figure 3. Alternating current behaviour of lansoprazole (20 µg mL^{-1}) in BRb of pH 7. Superimposed alternating voltage: 15 mV; frequency 75 Hz; phase angle 90˚. (SE: Supporting Electrolyte).

The diffusion-current constants (Id) were calculated at room temperature (25C˚) according to Ilkovic equation[34] for varying concentrations and were found to be 1.70 ± 0.01 (n = 6) and 1.66 ± 0.01 (n = 8) for LNS and OMP respectively, using the anodic DC_t mode. The results are shown in Table 4. The diffusion coefficients (D) were calculated using different concentrations of the drugs and were found to be 1.97×10^{-6} cm^2 sec^{-1} and 1.88×10^{-6} cm^2 sec^{-1} for LNS and OMP respectively. These small values may be attributed to the bulky nature of the depolarizers.

II. *Mechanism of the Electrode Reaction*

The number of electrons involved in the electrode reaction of both compounds was established via comparison of the waveheight of lansoprazole with that obtained from an equimolar solution of a previously studied compound with equal diffusion coefficient; namely, nilvaldipine[35]. In BRb of pH 7.0, both compounds gave one wave of the same height. It can be concluded therefore that, only the sulphoxide group is involved in the anodic process being oxidized into the corresponding sulphone group (Scheme 1). The following mechanism is postulated for the electrode reaction:



Scheme 1.

III. *Analytical Applications*

Figure 1 shows the typical anodic DC_t and DPP polarograms of lansoprazole in BRb of pH 7, respectively. The current is proportional to the concentration of the depolarizers over a convenient range. Both DC_t and DPP modes in the anodic technique were successfully applied to the assay of LNS and OMP whether *per se* or in dosage forms. Plots representing the relationship between the concentration of the studied compounds and the diffusion current give straight lines over the concentration range of 4-24, and 2-16 µg mL^{-1} using Direct Current (DC_t) mode for LNS and OMP, respectively and over the range 2-18 and 0.4-12 µg mL^{-1} using the Differential Pulse Polarographic (DPP) mode for LNS and OMP respectively. The lower detection limit (S/N = 2) were 0.2 µg mL^{-1} (5.41×10^{-7} M) and of 0.05 µg mL^{-1} (1.45×10^{-7} M) for LNS and OMP, respectively adopting the DPP technique (Table 2).

Linear regression analysis of the data gave the following equations:

(I) *For lansoprazole*

$$id = 4.5 \times 10^{-4} + 0.0055\ C \qquad (r = 0.9999,\ DC_t \text{ mode})$$

Table 2. Analytical parameters for the polarographic determination of lansoprazole and omeprazole using anodic DCt and DPP modes respectively

Parameter	Lansoprazole		Omeprazole	
	DC_t mode	DPP mode	DC_t mode	DPP mode
Concentration range (μg/mL)	4-24	2-18	2-16	0.4-12
Lower detection limit (M)	—	5.42×10^{-7}	—	1.45×10^{-7}
Correlation coefficient (r)	0.9999	0.9999	0.9999	0.9999
Slope	0.0055	0.0196	0.0058	0.031
Intercept	4.5×10^{-4}	1.536×10^{-3}	1.621×10^{-4}	3.593×10^{-4}
$S_{y/x}$*	2.048×10^{-4}	1.43×10^{-3}	3.503×10^{-4}	1.117×10^{-3}
S_a**	7.598×10^{-5}	9.36×10^{-3}	2.575×10^{-4}	7.977×10^{-4}
S_b***	1.224×10^{-5}	9.60×10^{-5}	2.703×10^{-5}	8.907×10^{-5}
% Error****	0.13	0.33	0.27	0.24

*$S_{y/x}$: Standard deviation of residuals.
**S_a: Standard deviation of intercept of regression line.
***S_b: Standard deviation of slope of regression line.
****% Error: RSD% / $\sqrt{n}$

Table 3. Polarographic analysis of lansoprazole and omeprazole in pure form using DCt and DPP modes respectively

Compound	DC_t mode	DPP mode	Reference methods[3,14]
Lansoprazole			
No. of Experiments	6	7	3
Mean found (%) ± SD	99.96 ± 0.33	100.03 ± 0.88	100.22 ± 0.53
Variance	0.11	0.77	0.28
Student's t-value	0.91 (2.37)	0.34 (2.31)	
Variance ratio F-test	2.42 (5.79)	2.76 (5.14)	
Omeprazole			
No. of Experiments	8	10	3
Mean found (%) ± SD	99.87 ± 0.76	99.58 ± 0.75	99.96 ± 0.91
Variance	0.58	0.56	0.83
Student's t-value	0.17 (2.26)	0.74 (2.20)	
Variance ratio F-test	1.43 (4.74)	1.47 (4.26)	

Figures in parentheses are the tabulated t and F values respectively at $p = 0.05$[36].

$$ip = 1.536 \times 10^{-3} + 0.019\ C \quad (r = 0.9999, \text{DPP mode})$$

(II) *For omeprazole*

$$id = 1.621 \times 10^{-4} + 0.0058\ C \quad (r = 0.9999, DC_t \text{ mode})$$
$$ip = 3.593 \times 10^{-4} + 0.031\ C \quad (r = 0.9999, \text{DPP mode})$$

where C is the concentration in μg mL^{-1}, id is the diffusion current (in μA) in the DC_t mode and ip is the current in the DPP mode respectively.

Statistical evaluation of the regression lines regarding the standard deviation of the residuals ($S_{y/x}$), the standard deviation of the intercept (S_a) and standard deviation of the slope (S_b) are also shown in Table 2. The small values of the figures point out to the high precision of the proposed method.

Statistical analysis of the results obtained by the proposed and reference methods[3,14], using the Student's t-test and Variance ratio F test, shows no significant difference between the performance of the two methods regarding the accuracy and precision, respectively[36]. The results are shown in Table 3.

Each of DC_t, DPP modes were successfully applied to the determination of LNS and OMP in commercial capsules (30 mg and 20 mg each) and the results obtained are abridged in Table 5. Capsule excipients such as starch, talc magnesium stearate, lactose, avisil and gelatin did not interfere with the assay.

As one of the possible pathways of degradation of these compounds is the oxidation of the sulphoxide group into the corresponding sulphone, the method can be therefore considered as stability-indicating assay for the two drugs.

CONCLUSION

A simple and fairly sensitive method was developed for the determination of lansoprazole and omeprazole in their capsules. The method has some distinct advantages over other existing methods regarding simplicity and time saving. The lower detection limits are 5.41×10^{-7} M and 1.45×10^{-7} M for LNS and OMP respectively using the DPP modes which are comparable to those reported by chromatographic methods[7]. The concentration range and the detection limit are comparable to those reported by recently published voltammetric method[30]. Moreover, the method can be considered as a stability-indicating assay for the two drugs.

ACKNOWLEDGMENTS

Dr. F. Belal would like to thank the Alexander von

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Table 4. Correlation between the concentration of lansoprazole, omeprazole and the diffusion current in the DCt mode

Compound	No.	Concentration (mM)	Current (μA)	id/C (μA/mM)	Id = id/ C $m^{2/3}$ $t^{1/6}$
Lansoprazole	1	1.083×10^{-2}	0.0225	2.077	1.714
	2	2.166×10^{-2}	0.0450	2.077	1.714
	3	3.249×10^{-2}	0.0667	2.054	1.695
	4	4.332×10^{-2}	0.0892	2.060	1.699
	5	5.415×10^{-2}	0.1110	2.049	1.691
	6	6.498×10^{-2}	0.1335	2.054	1.695
Mean				2.062	1.702
± SD				0.011	0.009
Omeprazole	1	5.79×10^{-3}	0.0117	2.021	1.667
	2	1.158×10^{-2}	0.0231	1.995	1.646
	3	1.737×10^{-2}	0.0351	2.021	1.667
	4	2.316×10^{-2}	0.0468	2.021	1.667
	5	2.895×10^{-2}	0.0590	2.038	1.682
	6	3.474×10^{-2}	0.0700	2.015	1.663
	7	4.053×10^{-2}	0.0815	2.011	1.659
	8	4.632×10^{-2}	0.0928	2.005	1.654
Mean				2.016	1.663
± SD				0.013	0011

Each result is the average of three separate determinations.

Table 5. Application of the proposed method to the analysis of the studied compounds in dosage forms

Pharmaceutical preparations	Recovery (%) of DC_t mode	Recovery (%) of DPP mode	Reference methods[3,14]
Lopral capsules[a]	99.38	100.15	101.56
(30 mg of lansoprazole/	101.50	99.58	98.83
capsule)	99.73	101.26	100.19
	101.32	101.48	
	102.02		
	101.63		
Mean found (%) ± SD	100.93 ± 0.99	100.61 ± 0.79	100.19 ± 1.11
t-value	1.02 (2.37)	0.59 (2.57)	
F-value	1.26 (5.79)	2.03 (9.55)	
Gasec capsules[b]	98.75	98.80	99.37
(20 mg of omeprazole/	99.16	100.80	101.72
capsule)	99.66	99.60	100.69
	99.75	101.00	
	100.46	99.57	
	99.09		
Mean found (%) ± SD	99.48 ± 0.61	99.95 ± 0.92	100.59 ± 1.18
t-value	2.10 (2.37)	0.89 (2.45)	
F-value	3.76 (5.79)	1.64 (6.94)	

Each result is the average of three separate determinations.
Figures in parentheses are the tabulated t and F values respectively at $p = 0.05$[36].
[a]Product of T3A, Assiut, Egypt.
[b]Product of Medical Union Pharmaceuticals Abu Sultan, Ismalia, Egypt.

Humboldt Foundation, Bonn, Germany, for kindly providing the instrument used in this study, to his department.

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