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Spectrophotometric determination of omeprazole, lansoprazole and pantoprazole in pharmaceutical formulations

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Abstract

The compensation method and other chemometric methods (derivative, orthogonal function and difference spectrophotometry) have been applied to the direct determination of omeprazole, lansoprazole and pantoprazole in their pharmaceutical preparations. The methods have been validated; the limits of detection were found to be 3.3×10^{-2}, 3.0×10^{-2} and 3.5×10^{-2} μg ml^{-1} for the three drugs, respectively. The repeatabililty of the methods were found to be 0.3–0.5%. The linearity ranges were found to be 0.5–3.5 μg ml^{-1}. The proposed methods have been applied to the determination of the three drugs in their grastro-resistant formulations. The difference spectrophotometric (ΔA) method is unaffected by the presence of acid induced degradation products; hence can be used as a stability indicating assay.

Keywords: Spectrophotometry; Compensation; Derivative; Orthogonal function; Difference spectrophotometry; Chemometrics; Omeprazole; Lanzoprazole; Pantoprazole

1. Introduction

Omeprazole, lansoprazole and pantoprazole belong to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the H^+/K^+ATPase enzyme system at the secretory surface of the gastric parietal cell [1]. They are used for the treatment of acid-peptic diseases such as duodenal, gastric and esophegeal ulceration [2].

Omeprazole is official in the USP 24 [3] and BP 98 [4]. Different colorimetric methods have been described for the determination of the three investigated drugs in their single component dosage forms based on their reactions with various reagents [5–8]. Omeprazole has been also assayed by the A_{max} method directly [9] and using a flow injection system [10]. A first derivative spectrophotometric method was developed for the determination of omeprazole in aqueous solution by measuring the derivative amplitude at 313 nm ($\Delta\lambda = 8$). The method has been described to be

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2.59 times more sensitive than the official HPLC method [11]. Omeprazole has also been determined in presence of its photodegradation product by derivative spectrophotometry (^{1}D, ^{2}D and ^{3}D) and complex formation [12]. Both lansoprazole and omeprazole have been analysed in their enteric coated granules using the second derivative spectrophotometric method at $N=9$, $\Delta\lambda=31.5$ [13,14]. A two-wavelength spectrophotometric method by measuring the peak-trough amplitude at 293 and 320 nm [15], has also been described.

Omeprazole has been also determined by direct current [16] differential pulse polarography [17] and adsorptive stripping voltammetry [18]. A DPP method has been reported to study the degradation of the same drug [19]. Different chromatographic techniques have been applied for the analysis of omeprazole capsules such as TLC densitometry [20], HPTLC [21] and HPLC [22–24]. The drug has also been determined by capillary electrophoresis [25] and indirect argentometric titration [26]. For pantoprazole and lansoprazole a TLC and HPTLC methods have been reported for their determination in pharmaceutical preparations [27,28]. The analysis of the three drugs in biological fluids has been mainly performed by HPLC techniques [29–31].

Being rapid and simple, spectrophotometry is one of the most extensively used analytical technique in drug analysis. However, excipients usually interfere in the direct spectrophotometric assay of dosage forms. The present work represents application of different spectrophotometric techniques viz compensation, derivative, orthogonal functions to eliminate excipient's interference for the determination of the three investigated drugs in their pharmaceutical preparations without prior separation. Two stability indicating methods are also proposed depending upon difference spectrophotometry.

1.1. Compensation method

The compensation method is a non-mathematical method for the detection and elimination of unwanted absorption during spectrophotometric analysis [32]. The method involves a comparison of several difference spectra (sample, s, reference, r) using different concentrations of a reference solution (c_r) in the reference cell. Hence if A_{si} and A_{ri} refer to the absorbances of the relevant cells against air at a wavelength, i, then $\Delta A = A_{si} - A_{ri}$. The characteristics of the pure compound, which may be observed in the difference curve, gradually decreases as C_r increases and finally disappears at the balance point, for which $C_r = C_s$. A further increase in C_r then leads to an over-compensated difference curve which exhibits an inversion of the pure compound's characteristic peak (Fig. 1).

1.2. Derivative spectrophotometry

The conversion of the zero-order UV spectrophotometry into higher order (first and second

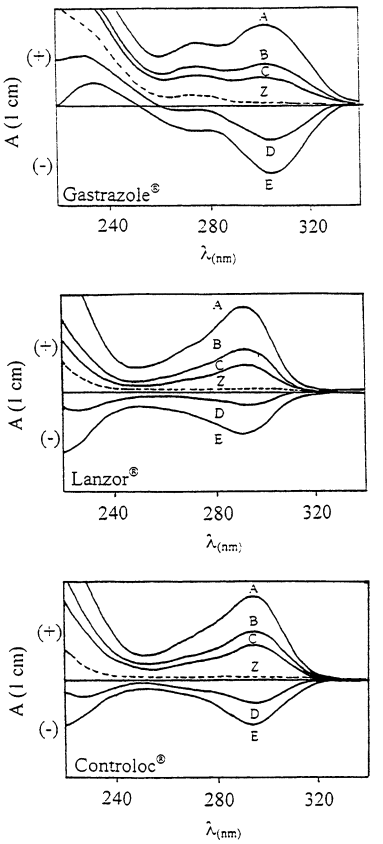

Fig. 1. (A) absorption curve of Gastrazole®, Lanzor®, Controloc®; (B and C) the difference curves obtained by compensation; (Z) the balance-point; and (D and E) over-compensated difference curves.

derivative) spectra resulted in elimination of the non specific matrix interference and considerably improved accuracy of the determination. If the irrelevant absorption is constant it could be eliminated even in the ^1D. While if the background is a linear or quadratric function of wavelength, the ^2D or ^3D or higher order derivative would eliminate such interference, respectively

1.3. Orthogonal functions method

Glenn's method of orthogonal function [33] has been extensively used to eliminate interference in spectrophotometric analysis. The interference can be corrected for by using a suitable polynomial, number of points wavelength range and intervals.

Convolution is a plot of p_j calculated at a specified set of equally spaced wavelengths versus λ_m where $\lambda_m = (\lambda_f + \lambda_i/2)$ m = mean of set of wavelengths f and i stand for final and initial wavelengths, respectively. A BASIC program has been used [34] for carrying out the convolution process for any number of points up to 100 points orthogonal polynomials from the constant to the quintic coefficients.

Recently [35], it was reported that calculation of orthogonal function coefficients give the analogous derivative order. Thus, calculation of quadratic coefficient p_2 is analogous to second order derivative ^2D, etc.

1.4. Difference spectrophotometry (ΔA)

The ΔA has been successfully used to eliminate interferences from gastro-resistant granules as well as from degradation products.

2. Experimental

2.1. Apparatus

A Perkin Elmer-Lambda EZ 201 spectrophotometer equiped with a Panasonic 24 pin KX-P 3626 printer was used.

2.2. Reagents and standard solutions

- Analytical grade of hydrochloric acid and sodium hydroxide were used.
- Omeprazole, lansoprazole and pantoprazole were kindly supplied by Impex Quimica, S.A. (Spain), Amriya (Alexandria, Egypt) and ByK Gulden Lamberg.

Gastrazol® capsules (Amriya (Alexandria, Egypt). Each capsule was labelled to contain 40 mg Omeprazole, starch, sucrose, eudragit L 100.

Lanzor® capsules (Hoechst Marrion Roussel). Each capsule was labeled to contain 15 mg Lansoprazole, magnesium carbonate, neutral microgranules (Saccharose and corn starch), saccharose, corn starch, low substitution hydroxypropyl cellulose, hydroxypropyl cellulose, endragit L 30 D-SS, talc, polyethyleneglycol, titanium dioxide, polysorbate 80, anhydrous colloidal silica.

Controloc® tablets (BYK) Kanstanz Germany. Each tablet was labeled to contain 45.1 mg pantoprazole sodium sesquihydrate equivalent to 40.0 mg pantoprazole, sodium carbonate, mannitol, crospovidone, polyvidone K 90, calcium stearate, hydroxypropyl methyl cellulose, polybidone K 25, titanium dioxide E 171/CI 77891. Yellow ferric oxide E 172/CI 77492, propylene glycol, eudragit L 30 D-55, sodium lauryl sulfate, polysarbate, triethyl citrate, printing ink (opa-code S-1-9210), dry residue.

- Stock standard solutions (100 mg%) of each drug was prepared in 0.1 M sodium hydroxide. Suitable dilutions were made using the same solvent. The solutions were found to bee stable for at least 4 days when stored in the refrigerator.
- Stock solutions of the degraded drugs were prepared by acidification of an aliquot from the stock standard solution with 0.1 M hydrochloric acid then appropriately diluted with either 0.1 M sodium hydroxide or 0.1 M hydrochloric acid, according to the case.

2.3. Preparation of sample solutions

For pantoprazole, ten tablets were ground and for omeperazole and lansoprazole the contents of ten capsules were mixed. A quantity of the resulted powder equivalent to about 50 mg drug was accurately weighed and transferred into a 100-ml volumetric flask using 0.1 M sodium hydroxide. The flask was half filled with the same solvent, shaken automatically for 15 min and then completed to the mark.

2.4. Spectrophotometric measurements

- Final solutions for measurements were prepared over the concentration ranges given in Table 1.
- The derivative spectra were recorded over the wavelength range of 220–340 nm. The amplitude of the derivative curve was measured at the selected wavelengths (Table 1).
- For the compensation method the absorbance difference spectra (sample versus reference) were recorded over the wavelength range of 220–340 nm, using different concentrations of the reference solution, prepared from the stock standard solution.
- For the ΔA method the absorbance difference spectra (intact drug versus degradation product) were recorded. The amplitude of the curve at the chosen wavelengths (Table 1) was measured.
- For the orthogonal function method the absorbances of each solution were measured at 2 nm interval over the wavelength range of 220–340 nm. The coefficients were calculated using a BASIC program [34].

3. Results and discussion

Omeprazole, lansoprazole and pantoprazole are acid labile [1]. The first two drugs are dispensed in the form of enteric-coated granules in capsules, while the latter is formulated as enteric-coated tablets.

The compensation method has been applied to detect the presence of irrelevant absorption, due to excipients interference. The latter has been detected at the balance point. (Fig. 1). Accordingly, the direct application of the conventional A_{max} method for the determination of the three drugs in their formulations will certainly lead to erroneous results.

Several spectrophotometric methods have been applied to correct for such irrelevant absorption. These are: derivative, orthogonal functions and difference spectrophotometry.

3.1. Compensation method

In view of the fact that location of the balance-point is subjective and in order to eliminate any personal bias, four analysts determined the exact balance-point independently of the three drugs (Fig. 1).

3.2. Derivative spectrophotometry

The compensation method proved that the irrelevant absorption curve is almost linear. Accordingly, it can be eliminated by recording derivative absorption curves and, in particular, second derivative spectra [34,35]. The ^{2}D amplitudes at 306.2, 292.4 and 295.4 nm has been chosen for the analysis of omeprazole, lansoprazole and pantoprazole, respectively where excipients showed nil contribution (Fig. 2).

3.3. Orthogonal functions method to generate derivative curves

The irrelevant absorption was nearly rectilinear from about 290 to 320 nm for omeprazole and from about 260 to 320 nm for lansoprazole and pantoprazole preparations. This suggested that the orthogonal functions method could be used to correct for it. For the determination of the three drugs the quadratic polynomial, P_2 has been selected; with 10 points (4 nm intervals), 6 points (6 nm intervals) and 8 points (6 nm intervals) for omeprazole, lansoprazole and pantoprazole, respectively. In each case the quadratic coefficient, p_2, was maximum for the drug and negligibly small for the irrelevant absorption. The comparative coefficients p_2, at the selected λ_{me} (306, 293 and

Table 1
Validation of the proposed methods

	Omeprazole	Lansoprazole	Pantoprazole
^2D (second derivative)			
λ (nm)	306.2	292.4	295.4
Concentration range (mg/100 ml)	0.2–4.2	0.2-4	0.2–4.2
a	-1.23×10^{-3}	3.87×10^{-4}	-6.52×10^{-4}
b	0.521	0.677	0.534
S_b^2	3.051×10^{-7}	2.137×10^{-6}	8.351×10^{-7}
R	0.99999	0.99998	0.99998
Repeatability (RSD(%))	0.510	0.391	0.363
Orthogonal function (Q_2)			
Number of points	10	6	8
Wavelength interval (nm)	4	6	6
λ mean (nm)	306	293	295
Concentration range (mg%)	0.5–3.5	0.5–3.5	0.5–4.2
A	-0.32×10^{-3}	-0.49×10^{-3}	-0.44×10^{-3}
B	268.450×10^{-3}	251.245×10^{-3}	284.431×10^{-3}
S_b^2	0.136×10^{-6}	0.327×10^{-6}	0.180×10^{-6}
R	0.99999	0.99998	0.99999
Repeatability (RSD(%))	0.365	0.383	0.264
ΔA (Intact vs. deg. in NaOH)			
λ (nm)	256	254	254, 256
Concentration range (mg%)	0.5–4	0.7–3.5	0.7–4.2 mg%
A	-1.04×10^{-3}	6.12×10^{-4}	-1.96×10^{-3}
B	0.221	0.232	0.191
S_b^2	1.500×10^{-6}	1.078×10^{-5}	2.276×10^{-6}
R	0.99988	0.99941	0.99974
Repeatability (RSD(%))	0.433	0.861	0.460
ΔA (Intact vs. deg. in HCl)			
λ (nm)	280	250	250
Concentration range (mg%)	0.7–4	0.7–3.5	0.5–4.2
A	2.56×10^{-3}	-3.11×10^{-3}	-1.69×10^{-3}
B	0.125	0.207	0.131
S_b^2	1.027×10^{-6}	1.611×10^{-6}	9.569×10^{-7}
R	0.99982	0.99989	0.99976
Repeatability (RSD(%))	0.519	0.516	0.512

295 nm respectively) were found to bee highly reproducible and proportional to the drugs concentration (Table 1) and showed negligible contribution for the irrelevant absorption (Fig. 3).

It is noteworthy to mention that the analytical wavelengths (optima) for ^{2}D and p_2 were found to be 306.2 and 306 nm for omeprazole, 292.4 and 293 nm for lansoprazole and 295.4 and 295 nm for pantoprazole, respectively. This supports that convoluted absorption curves are analogous to derivative absorption curve.

3.4. ΔA method

Omeprazole, lansoprazole and pantoprazole are acid-labile. Fig. 4aFig. 5aFig. 6a show the absorption spectra of the intact drug in 0.1 M sodium hydroxide and the acid-degradation product in 0.1 M sodium hydroxide and 0.1 M hydrochloric acid. The spectra of the UV absorbing excipients which are commonly used for the formulation of gastro-resistant granules are generally independent of pH. The ΔA (intact drug in NaOH versus degraded (by

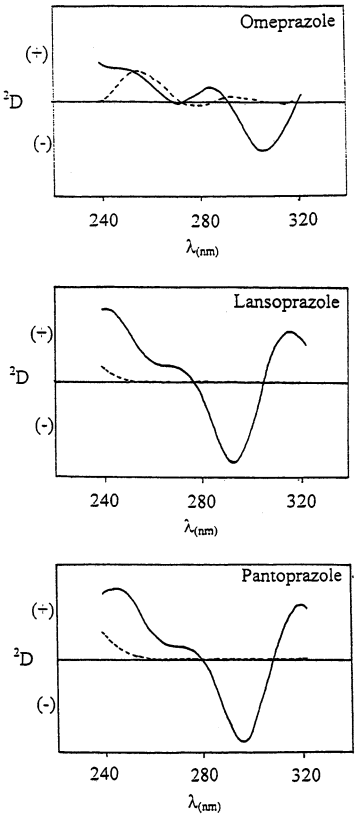

Fig. 2. Second derivative spectra of 1 mg% drug (—) and dosage form excipients (---).

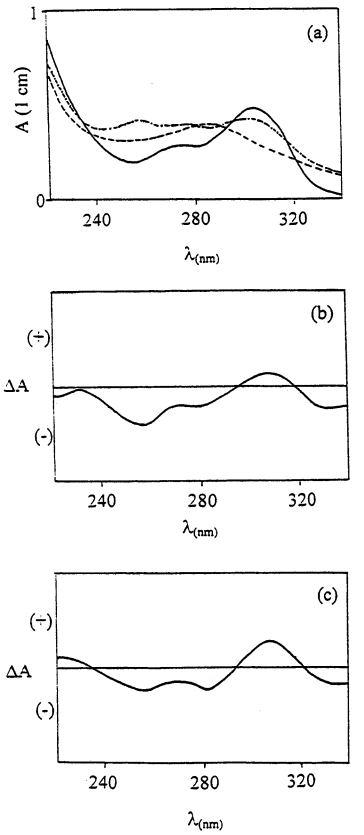

Fig. 4. (a) Absorption spectra of 1 mg% omeprazole in NaOH (—) and its acid induced degradation product in NaOH (- · - · -) and in HCl (---). (b) ΔA (intact drug in NaOH vs. acid induced degradation product in NaOH). (c) ΔA (intact drug in NaOH vs. acid induced degradation product in HCl).

0.1 M HCl) in NaOH and intact in NaOH vs. degraded in HCl) method could be used for the determination of each drug in its pharmaceutical preparation. Of the various possibilities offered by the ΔA spectra (Fig. 4b,cFig. 5b,cFig. 6b,c) the

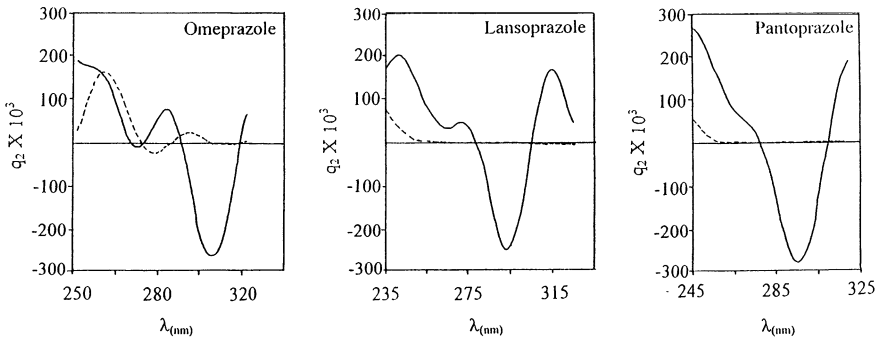

Fig. 3. p_2 convoluted curves of 1 mg% drug (—) and dosage form excipients (---).

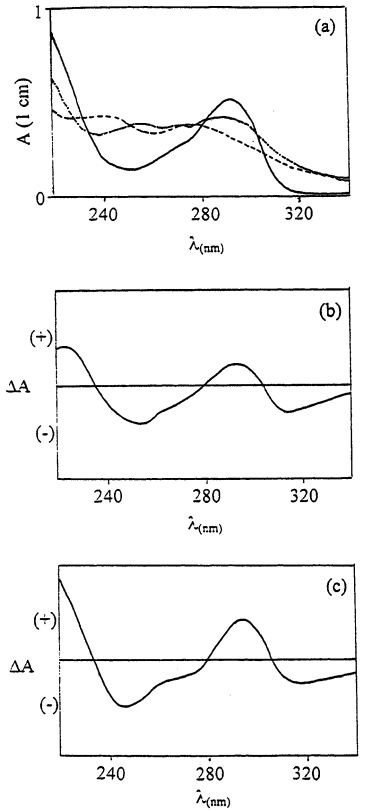

Fig. 5. (a) Absorption spectra of 1 mg% lansoprazole in NaOH (—) and its acid induced degradation product in NaOH (- ·- · -) and in HCl (---). (b) ΔA (intact drug in NaOH vs. acid induced degradation product in NaOH). (c) ΔA (intact drug in NaOH-acid induced degradation product in HCl).

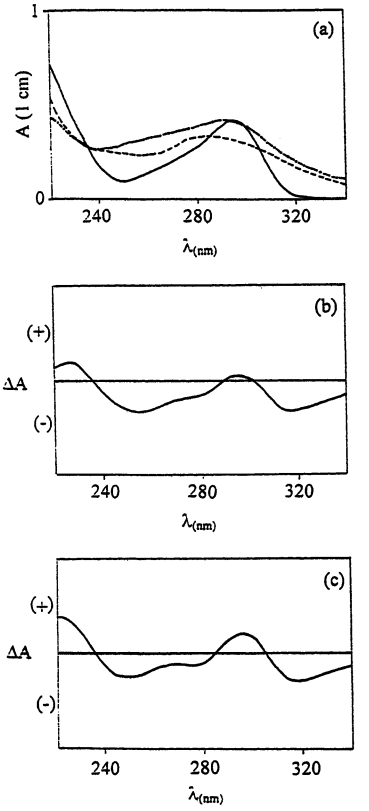

Fig. 6. (a) Absorption spectra of 1 mg% pantoprazole in NaOH (—) and its acid induced degradation product in NaOH (- ·-· -) and in HCl (---). (b) ΔA (intact drug in NaOH vs. acid induced degradation product in NaOH). (c) ΔA (intact drug in NaOH vs. acid induced degradation product in HCl).

amplitudes at the wavelengths cited in Table 1 have been selected for the quantitative analysis.

3.5. Stability indicating assays

3.5.1. Using ΔA (intact in NaOH versus degraded (by 0.1 M HCl) in NaOH)

It is well known that the three investigated drugs undergo rapid degradation when acidified. The proposed ΔA method (intact drug in NaOH vs. degraded in NaOH) has been applied for the determination of the drugs in pharmaceutical dosage forms in the presence of their acid induced degradation product in 0.1 M sodium hydroxide. The absorbance difference at the selected wavelengths (Table 1) is proportional to the drug concentration and independent to the degradation product.

3.5.2. Using isosbestic point (intact in NaOH versus degraded in HCl)

The acid induced degradation products of the three drugs exhibited different absorption spectra in NaOH and HCl (Fig. 4aFig. 5aFig. 6a). The ΔA method (intact drug in NaOH versus degraded in HCl) has been applied as stability indicating assay for omeprazole and lansoprazole as the absorption spectra of the degraded products in HCl and NaOH exhibited isosbestic points at 280 and 250 nm, respectively; meanwhile, their ΔA curves exhibited troughs (Fig. 4aFig. 5a). Unfortunately, degraded pantoprazole spectra in NaOH and HCl

showed no isosbestic points (Fig. 6a). Accordingly, the ΔA method (intact drug in NaOH versus degraded in HCl) could not be used for the selective determination of the drug in presence of its degradation product.

3.5.3. Analysis of laboratory-made mixtures

In order to check the applicability of the proposed ΔA methods as stability indicating assay intact drugs were determined in several mixtures containing different concentrations of the degradation products. Table 2 shows the results of the determination of such mixtures. Satisfactory results were obtained for the recovery of the intact drugs, indicating that the ΔA method (intact drug in NaOH versus degraded in NaOH) is effective for the selective determination of the three drugs in presence of their acid induced degradation product. The ΔA method (intact drug in NaOH vs. degraded in HCl) is satisfactory only for omeprazole and lansoprasole.

Table 2
Assay results of the investigated drugs in presence of its acid induced degradation product in laboratory made mixtures by ΔA method

Ratio degraded: drug	Recovery (%)		
	Omeprazole	Lansoprazole	Pantoprazole
1. *Intact drug in 0.1 M NaOH vs. degraded in 0.1 M NaOH*			
1:1.01	99.9	99.1	100.4
1:1.05	100.6	100.2	100.9
1:1.10	100.1	98.9	101.2
1:1.30	99.7	99.6	99.9
1:1.50	100.1	99.8	100.7
1:1.60	99.9	100.4	100.4
1:1.75	100.4	100.0	100.2
Mean	100.1	99.7	100.5
±S.D.	0.31	0.56	0.44
2. *Intact drug in 0.1 M NaOH vs. degraded in 0.1 M HCl*			
1:1.01	100.7	99.0	
1:1.05	99.9	99.8	
1:1.10	101.5	99.3	
1:1.30	100.7	100.0	
1:1.40	101.1	98.8	
1:1.50	100.3	99.5	
Mean	100.7	99.4	
±S.D.	0.57	0.46	

3.6. Validation of the proposed methods

3.6.1. Linearity

A critical evaluation of the ^{2}D, orthogonal function and ΔA methods was performed by the statistical analysis of the experimental data. The good linearity of the calibration graphs and negligible scatter of the experimental points is clearly evident by the values of the correlation coefficients and variances around the slopes (Table 1).

3.6.2. Repeatability

In order to study the precision of the proposed methods, six replicates measurements were carried out for three different concentrations of each drug. The results are summarized in Table 1. The relative standard deviations did not exceed 1% indicating high precision of the methods.

3.6.3. Accuracy

The second derivative method and the orthogonal function method depend upon the absorption characteristics of the irrelevant absorption curve obtained by the compensation method. These methods are based on the assumption that the interferences absorption curves possess none of the absorption characteristics of the investigated compounds. The other two stability indicating methods depend upon the absorption characteristics of the acid induced degradation products of each of the three compounds.

There were non-significant differences between the results obtained by the applied methods for the determination of the investigated compounds (Table 3). Accordingly, all proposed methods can validate each other with respect to accuracy for dosage forms.

3.6.4. Specificity

The compensation, derivative curve and the orthogonal function methods are selective for the investigated compounds when standard and test solutions are compared with each others with regard to general shape and position of the optimum wavelength. The ^{2}D optima occur at 306.2, 292.4 and 295.4 nm and the p_2 optima occur 306, 293 and 295 nm for omeprazole lansoprazole

Table 3
Assay results of the investigated drugs in their pharmaceutical preparations

Commercial product	Percentage found					
	A_{max} [a]	Compensation ($n=4$)	^2D [a]	p_2 [a]	ΔA [a]	
					NaOH vs. NaOH	NaOH vs. HCl
Gastrazole® [b] capsules						
Mean	105.2	100.0	100.3	100.6	100.2	100.2
±S.D.	0.40	Zero	0.39	0.42	0.50	0.55
Variance	0.16	Zero	0.15	0.18	0.25	0.30
RSD%	0.38	Zero	0.39	0.42	0.50	0.55
t [c]				(1.49)		
F [c]					(2.00)	
Lanzor® [b] capsules						
Mean	104.4	100.0	99.9	100.0	100.2	100.1
±S.D.	0.46	Zero	0.44	0.35	0.45	0.53
Variance	0.21	Zero	0.19	0.212	0.20	0.28
RSD%	0.44	Zero	0.44	0.35	0.45	0.53
t [c]				(1.18)		
F [c]					(2.33)	
Controloc® [b] tablets						
Mean	108.0	105.2	105.3	105.0	105.3	105.4
±S.D.	0.48	0.36	0.39	0.41	0.51	0.51
Variance	0.23	0.13	0.15	0.17	0.26	0.26
RSD%	0.44	0.34	0.37	0.39	0.48	0.48
t [c]					(1.49)	
F [c]				(1.73)		

[a] Mean of six experiments.
[b] Gastrazole® capsules labelled to contain 20 mg omeprazole per capsule. Lanzor® capsules labelled to contain 15 mg lansoprazole per capsule. Controloc® tablets labelled to contain 451 mg pantoprazole sesquihydrate per tablet.
[c] Theoretical t (0.05) = 2.23 and F (0.05) = 5.05.

and pantoprazole, for both test and solutions, respectively.

The difference absorption spectrum in (0.1 M hydrochloric acid vs. 0.1 M sodium hydroxide) is highly characteristic for each investigated compound (Figs. 4–6). The interferences do not possess any of their absorption characteristics. According to ICH document for specificity, the methods are specific in presence of the matrix component.

3.6.5. Limit of detection (LOD) and limit of quantitation (LOQ)

The determination of the LOD has been performed experimentally by the detection of absorption peak of each drug and was found to be 3.3×10^{-2}, 3.0×10^{-2} and 3.5×10^{-2} μg ml^{-} for omeprazole, lansoprazole and pantoprazole, respectively. The LOQ at a RSD = 2% were 8×10^{-2}, 7.5×10^{-2} and 9×10^{-2} μg ml^{-} for the three drugs, respectively.

3.7. Analysis of pharmaceutical formulations

Using the previously mentioned selected parameters, the proposed methods (compensation, derivative, orthogonal functions and difference spectrophotometry) have been applied to the analysis of the three investigated drugs in their available pharmaceutical preparations. The results obtained are listed in Table 3. The results of these methods were compared statistically using t- and F-tests between the smallest and highest mean percentage recoveries and variances. The calcu-

lated values were not exceeded the theoretical ones, therefore, there is no significant difference between the proposed metrods of analysis with reqards to accuracy (t-test) and repeatability (F-test).

4. Conclusion

Colorimetric methods are time consuming and need special reagents. The A_{max} method [9] has been proved to be inaccurate due to matrix interference. Castro et al. [11] reported that the other methods are not stability indicating, while the present methods using difference spectrophotometry eliminate acid induced degradation products proved to be stability indicating. The spectrophotometric methods are more versatile and easy to apply than the polarographic and voltammetric methods [16,19]. The chromatographic methods need special equipment that may not be available in certain Q. C. laboratories. The disadvantage of the proposed methods is that they cannot be applied to biological fluids containing these compounds and their conjugated forms.

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